

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

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SMITH KLINE & FRENCH LABORATORIES, )  
LTD, and SMITHKLINE BEECHAM CORP., )  
d/b/a GLAXOSMITHKLINE, ) Civil Action No: 05-197 GMS  
)  
Plaintiffs, )  
)  
v. )  
)  
TEVA PHARMACEUTICALS U.S.A., INC., ) **FILED UNDER SEAL**  
)  
Defendant. )  
)

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**EXHIBIT 21 TO PROPOSED PRETRIAL ORDER:  
DEFENDANT'S [PROPOSED] FINDINGS OF FACT  
AND CONCLUSIONS OF LAW**

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**TABLE OF CONTENTS****FINDINGS OF FACT**

I.	THE PARTIES AND NATURE OF THE CASE.....	1
II.	PROCEDURAL BACKGROUND.....	1
III.	TECHNICAL BACKGROUND.....	3
	A.    Dopamine.....	3
	B.    Parkinson's Disease Is Characterized By A Lack Of Dopamine.....	5
	C.    Dopamine Agonists To Treat Parkinson's Disease .....	6
IV.	PATENTS-IN-SUIT .....	7
	A.    The '808 Patent Covers Certain Dopamine Agonist Compounds .....	7
	B.    The '860 Patent Covers The Use Of The '808 Compounds To Treat Parkinson's Disease .....	13

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## **CONCLUSIONS OF LAW AND UNDERLYING FACTS**

	<b>VI. LEGAL STANDARDS FOR PATENT INVALIDITY .....</b>	<b>21</b>
A.	Priority and Definition of Prior Art .....	21
B.	Anticipation.....	22
C.	Obviousness .....	23
<b>VII. CLAIM 5 OF THE '808 PATENT IS INVALID FOR OBVIOUSNESS.....</b>		<b>27</b>
A.	Field Of The '808 Patent Is Structure-Activity Relationships For Developing Dopamine Agonist Compounds .....	27
B.	Level Of Ordinary Skill In The Art Of The '808 Patent.....	29
C.	Date of Invention for Purposes of Prior Art.....	29
D.	Claim 5 Is Obvious In View Of The '944 Patent And The Prior Art Showing The "Supposedly Essential 7-Hydroxy" Was Not Essential .....	29
1.	The Scope And Content Of The Prior Art And The Differences From Claim 5.....	31
2.	The Subject Matter Of Claim 5 Would Have Been Obvious In View Of The '944 Patent And The Prior Art.....	36
E.	Claim 5 Is Invalid As Obvious In Light Of The 1981 Cannon Article And The Prior Art Teaching The Use Of Indolone Ring Systems .....	37
F.	The Secondary Considerations Of Non-Obviousness Do Not Reflect Non-Obviousness Of The '808 Patent .....	39
<b>VIII. CLAIM 3 OF THE '860 PATENT IS INVALID AS ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '808 PATENT AND OTHER PRIOR ART .....</b>		<b>41</b>
A.	Field Of The '860 Patent Is Pharmacology Of D <sub>2</sub> Dopamine Agonists .....	41
B.	Level of Ordinary Skill In The Art Of The '860 Patent .....	41
C.	Assertion Of "Unexpected" Central D <sub>2</sub> Activity In The '860 Patent Is Based On Scientifically Improper and Misinterpreted Tests.....	41

D.	Claim 3 Of The '860 Patent Is Anticipated By The '808 Patent .....	43
E.	In The Alternative, Claim 3 Of The '860 Patent Is Obvious .....	44
1.	Scope and Content Of Prior Art.....	45
a.	'808 Patent .....	45
b.	Cannon 1981 Article.....	45
c.	Cannon 1986 Article.....	46
d.	Cannon 1978 Article.....	47
2.	Claim 3 Of The '860 Patent Is Obvious.....	47
a.	Claim 3 Is Obvious In View Of The '808 Patent Combined With The Cannon 1981 Article And/Or The Cannon 1986 Article .....	47
b.	Claim 3 Is Obvious In View Of The '808 Patent Combined With The Cannon 1978 Article.....	48
F.	Secondary Considerations Of Non-Obviousness Do Not Show Claim 3 Of The '860 Patent Is Non-Obvious .....	48

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X.	LEGAL STANDARDS FOR INEQUITABLE CONDUCT.....	53
A.	Inequitable Conduct.....	53
B.	Materiality.....	54
C.	Intent to deceive.....	55

D. Patentability Issues Related To Teva's Inequitable Conduct Defenses.....	56
1. Inventorship .....	56
2. Utility/Enablement.....	58
 XI. THE '808 PATENT IS UNENFORCEABLE FOR INEQUITABLE CONDUCT .....	59
[REDACTED]	
[REDACTED]	
[REDACTED]	
 XII. THE '860 PATENT IS UNENFORCEABLE FOR INEQUITABLE CONDUCT .....	74
[REDACTED]	
[REDACTED]	
 XIII. CONCLUSION.....	80

## **FINDINGS OF FACT**

### **I. THE PARTIES AND NATURE OF THE CASE**

1. In this patent infringement case, Smith Kline & French Laboratories Ltd. and SmithKline Beecham Corp., d/b/a GlaxoSmithKline (collectively, "GSK") seek to prevent Teva Pharmaceuticals USA, Inc. ("Teva") from introducing a generic version of ropinirole hydrochloride tablets until after the two patents that GSK has asserted in this case expire. Teva contends that the two patents are invalid and are unenforceable for inequitable conduct and, for either reason, Teva should be permitted to market its tablets free of interference from GSK. The following are the Court's findings of fact and conclusions of law on these issues.

### **II. PROCEDURAL BACKGROUND**

2. This is a patent infringement action. GSK has asserted that Teva infringed two of GSK's patents when Teva filed an Abbreviated New Drug Application ("ANDA") with a Paragraph IV certification consistent with the relevant provisions in the Hatch-Waxman Act. These types of cases typically involve: (a) a proprietary product sold by a branded pharmaceutical company that is protected by patents the branded pharmaceutical company has listed in the Food And Drug Administration Center For Drug Evaluation And Research Approved Drug Products With Therapeutic Equivalence Evaluations (the "Orange Book"); and (b) a pharmaceutical company that seeks to market a generic version of the proprietary product before the expiration of the listed patents by filing an ANDA certifying the patents are invalid or not infringed. That is precisely the case here.

3. In this case, GSK is the branded pharmaceutical manufacturer. The proprietary drug it markets is Requip, a treatment for the signs and symptoms of idiopathic Parkinson's disease. The active ingredient in Requip is a compound known as ropinirole hydrochloride. GSK has listed two patents in the Orange Book as protecting its Requip drug product. The first

patent, U.S. Patent No. 4,452,808 (“the ‘808 patent”), has claims that cover thousands of allegedly dopaminergic compounds, including ropinirole hydrochloride, the active ingredient in Requip. The second patent, U.S. Patent No. 4,824,860 (“the ‘860 patent”), has claims that cover the use of many of these same compounds recited in the ‘808 patent, including ropinirole hydrochloride, for the treatment of Parkinson’s disease.

4. Teva is a pharmaceutical company that filed an ANDA seeking approval to market a generic ropinirole hydrochloride drug product for treatment of the signs and symptoms of idiopathic Parkinson’s disease. Teva provided the requisite notice to GSK, and in response, GSK filed this lawsuit for infringement of the ‘808 and ‘860 patents within the prescribed statutory period.

5. The parties have reached agreement on several issues solely for purposes of this action. The parties agree that jurisdiction and venue are proper, and the Court agrees. Teva does not dispute that GSK owns all right title and interest in the patents-in-suit (without prejudice to its arguments of improper inventorship). GSK asserts infringement of only claim 5 of the ‘808 patent and only claim 3 of the ‘860 patent and Teva agrees that the ropinirole hydrochloride tablets that are the subject of its ANDA would infringe if these claims are found to be valid and enforceable. GSK does not assert that Teva’s alleged infringement was willful.

6. The following issues are before the Court to decide: (1) is claim 5 of the ‘808 patent invalid for obviousness under 35 U.S.C. § 103; (2) is claim 3 of the ‘860 patent invalid as anticipated under 35 U.S.C. § 102; (3) is claim 3 of the ‘860 patent invalid for obviousness under 35 USC § 103; (4) if claim 3 is not invalid in view of the prior art, is claim 3 invalid under 35 U.S.C. §§ 102(f) and/or 103; (5) is the ‘808 patent unenforceable for inequitable conduct; and (6) is the ‘860 patent unenforceable for inequitable conduct. The Court first considers the invalidity

issues, followed by the inequitable conduct issues. Before discussing either, however, some discussion of the technical background is appropriate to provide context to the analysis.

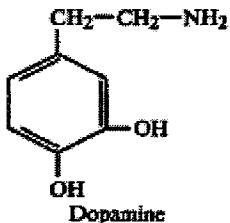
### **III. TECHNICAL BACKGROUND**

7. This case involves a treatment for the signs and symptoms of idiopathic Parkinson's disease. Parkinson's disease is a neurological disorder characterized by a dopamine deficiency that causes the patient to lose smooth motor control. Dopamine is a chemical that acts as a neurotransmitter in the central nervous system ("CNS") and peripheral nervous system. In the CNS—the nervous system comprising the brain and spinal cord—dopamine, among other things, transmits signals between neurons to regulate smooth motor control. In patients suffering from Parkinson's disease, the brain lacks sufficient dopamine to properly regulate smooth motor control. This results in involuntary movement, including, for example, the shaking and facial distortions that are commonly associated with Parkinson's disease.

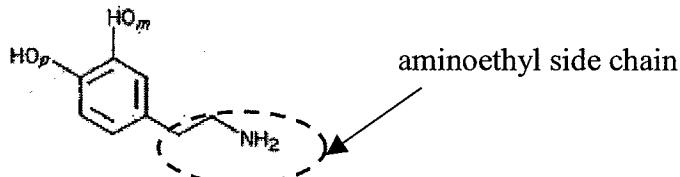
8. There is no known cure for Parkinson's disease. There are, however, treatments for the symptoms associated with Parkinson's disease. Ropinirole hydrochloride is one of those treatments. Ropinirole hydrochloride is a type of dopamine agonist (*i.e.*, a chemical that mimics dopamine in the body). There are many types of dopamine agonists. To understand what a dopamine agonist is, it is helpful to first understand some basics about dopamine.

#### **A. Dopamine**

9. At its most basic, dopamine is a chemical molecule that is produced naturally in the body. The dopamine molecule is represented by the following chemical structure, as shown in column 1 of the '808 patent:

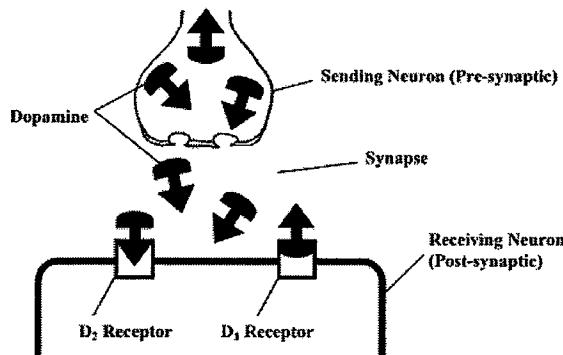


The same molecule can also be properly depicted as follows using standard chemical nomenclature:



As shown above, the dopamine chemical structure is defined by a six-sided benzene ring with an aminoethyl side chain and two hydroxy (or OH) groups. In dopamine, one of the hydroxy groups (shown as  $\text{HO}_p$  in the figure above) is located at the “para” position (*i.e.*, across from the side chain) and the other (shown as  $\text{HO}_m$  in the figure above) is located at a “meta” position (*i.e.*, two positions away from the aminoethyl side chain).

10. One of dopamine’s most important functions in the body is to act as a neurotransmitter. As illustrated below, a neurotransmitter sends signals between a neuron (“sending neuron”) and another neuron or organ (“receiving neuron or organ”) across a synapse (the space between the transmitting neuron (pre-synaptic) and the receiving neuron or organ (post-synaptic)).



11. To send a signal, the sending neuron receives an electrical pulse indicating the need to send a signal. The electrical pulse causes the sending neuron to release the neurotransmitter (*e.g.*, dopamine) into the synapse. The neurotransmitter crosses the synapse and interacts with corresponding receptors on the receiving neuron or organ. When the neurotransmitter binds to a corresponding receptor on the receiving neuron or organ, a resulting electrical pulse is sent along the receiving neuron or organ.

12. Like other neurotransmitters, dopamine acts on neuron and organ receptors. There are currently five known types of dopamine receptors. At the time of these inventions, dopamine receptors were classified as either D<sub>1</sub> or D<sub>2</sub> receptors. Subsequently, these two general “types” of receptors have been described as covering five separate dopamine receptors. For general purposes, these five dopamine receptors can be divided into two primary types: D<sub>1</sub>-type receptors and D<sub>2</sub>-type receptors. D<sub>1</sub>-type receptors can be found, for example, at post-synaptic sites in the renal (kidney) vascular bed within the peripheral nervous system. D<sub>2</sub>-type receptors can be found, for example, at post-synaptic sites in the CNS (including the brain) and at pre-synaptic sites in various locations in the peripheral nervous system (*e.g.*, in the cardioaccelerator nerve controlling heart rate).

#### **B. Parkinson's Disease Is Characterized By A Lack Of Dopamine**

13. Smooth motor control is associated with D<sub>2</sub>-type receptors in the brain. Dopamine is produced in the brain by the substantia nigra. In patients suffering from Parkinson's disease, the dopamine-producing neurons in the substantia nigra are destroyed. Without sufficient dopamine in the brain, the body cannot properly send signals across to the post-synaptic D<sub>2</sub>-type receptors, and as a result, cannot properly control smooth motor function.

14. Since Parkinson's disease is characterized by a dopamine deficiency in the brain, it may seem intuitive that the treatment would simply be administration of dopamine to replace

dopamine that is no longer naturally produced in the brain. However, administration of dopamine itself is not an effective treatment for Parkinson's disease. This is because dopamine's chemical structure—a catechol—impedes its permeation across the blood-brain barrier that separates the brain from the blood that circulates through the rest of the body. Thus, dopamine that is administered to a patient by any conventional method (e.g., oral, injection, etc.) will not reach the brain, where it is needed.

15. Instead, the primary treatment for Parkinson's symptoms is administration of levodopa (or "L-dopa"). L-dopa is a chemical precursor of dopamine that is metabolized to form dopamine in the human body. Unlike dopamine, L-dopa does cross the blood-brain barrier. When administered to Parkinson's disease patients, some amount of the intact L-dopa crosses the blood-brain barrier and is metabolized to form dopamine in the brain. This treatment has successfully been used since the 1950's, and remains the "gold standard" for treating Parkinson's disease today.

#### **C. Dopamine Agonists To Treat Parkinson's Disease**

16. A second approach to treating Parkinson's disease is the administration of dopamine agonists, like ropinirole hydrochloride. As discussed above, a dopamine agonist is a chemical that mimics dopamine for purposes of binding to receptors. Dopamine agonists can be designed to cross the blood-brain barrier and act in place of dopamine in the brain.

17. There has been substantial research about dopamine agonists. One important consideration for scientists developing dopamine agonists is determining what parts of the dopamine chemical structure account for its activity. Knowing what parts of the chemical structure are necessary to mimic dopamine allows scientists to make different test compounds that retain the essential features needed to mimic dopamine while including chemical substitutions for unnecessary parts of the dopamine molecule to attempt to enhance the

compound's properties as a drug—for example, its ability to be administered orally or cross the blood-brain barrier—without eliminating the drug's efficacy. This correlation between the structures of molecules and their activity, receptor selectivity, and other characteristics is known as structure-activity relationships. In the patent, the art of developing structure-activity relationships for dopamine agonists is referred to as the “structure function art.”

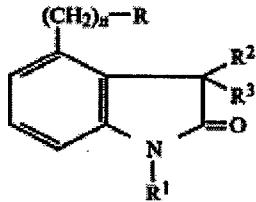
18. As a result of scientists working in the field of structure-activity relationships for the dopamine agonists, there are many different known dopamine agonists having different combinations of pharmacological properties. For example, it has long been known that dopamine agonists that bind to D<sub>2</sub> receptors (*i.e.*, D<sub>2</sub> dopamine agonists) in the brain can be an effective treatment for the symptoms of Parkinson's disease. In fact, administration of D<sub>2</sub> dopamine agonists to treat Parkinson's symptoms dates back to at least 1974. Among the D<sub>2</sub> dopamine agonists currently used to treat Parkinson's disease are bromocriptine (marketed as Parlodel, Pravidel, Lactismine), pergolide (marketed as Permax, Celance, and Pharken), and pramipexole (marketed as Mirapex, Mirapexin, Mirapexol, Firol, and Sifrol).

#### **IV. PATENTS-IN-SUIT**

##### **A. The '808 Patent Covers Certain Dopamine Agonist Compounds**

19. GSK's '808 patent, entitled “4-aminoalkyl-2(3H)-indolones,” is directed to an allegedly new type of dopamine agonist compound. It was filed on December 7, 1982 and names Mr. Gregory Gallagher as its sole inventor. Mr. Gallagher was a medicinal chemist at GSK.

20. The dopamine agonist compounds that are the subject of the '808 patent are based on a common chemical structure.



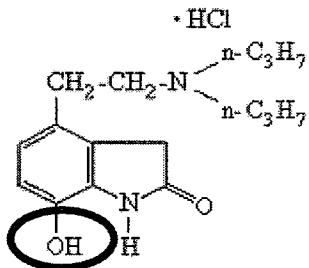
Significantly, there are *thousands* of dopamine agonist compounds that are described and claimed in the '808 patent as falling within the scope of this common chemical structure. This is because of the numerous different substituents that are disclosed for possible substitution at the various "R" positions shown in the figure above and the use of the variable "n" to denote the length of the side chain (represented as "(CH<sub>2</sub>)<sub>n</sub>—R" in the figure above). For example, claim 1 recites the common structure and claims all of the following variations as within its scope:

n is 1-3;

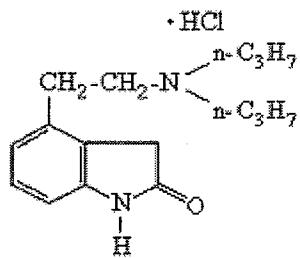
R is amino, C<sub>1-6</sub>-lower alkylamino, di-(C<sub>1-6</sub>-lower alkyl)amino, allylamino, diallylamino, N-(C<sub>1-6</sub>-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl) amino, and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are, each, hydrogen or C<sub>1-4</sub>-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

Any combination of these variables constitutes a dopamine agonist compound within the scope of the '808 patent.

21. The chemical structure of the preferred embodiment of the '808 patent is the direct descendant of the preferred compound disclosed in a prior art GSK patent, U.S. Patent No. 4,314,944. In fact, the preferred embodiment of the '808 patent is identical to the preferred embodiment of the prior art '944 in all respects but one—the '944 patent requires a hydroxy group at the para position (circled below) on the benzene ring while ropinirole, the preferred '808 patent compound has no hydroxy group at that position.



'944 Patent Compound



'808 Patent Compound

22. The '808 patent asserts that the various dopamine agonist compounds it claims have beneficial cardiovascular effects: the compounds "have utility, as specific dopamine agonists, in the treatment of disorders of the cardiovascular system, especially to treat hypertension, to treat angina pectoris, to treat the symptoms of congestive heart failure or to improve kidney function." ('808 patent, col. 4, ll. 26-30.) According to the '808 patent, these cardiovascular effects arise because the compounds are dopamine agonists for the D<sub>2</sub> receptor: "Activation of the D<sub>2</sub>-receptors on the sympathetic nerve terminals inhibits the release of noradrenaline, thereby promoting vasodilation, among other beneficial cardiovascular actions." ('808 patent, col. 4, ll. 40-44.) "The method of this invention for producing D<sub>2</sub> agonist activity manifests itself by inducing renal vasodilation [*i.e.*, causing constriction of the blood vessels in the kidney], anti-anginal [*i.e.*, preventing chest pain caused by lack of oxygen to the heart muscle], anti-hypertensive [*i.e.*, lowering blood pressure], and bradycardic activity [*i.e.*, slowing of the heart rate]." ('808 patent, col. 5, ll. 43-46.)

23. These same cardiovascular benefits are described with respect to the prior art '944 patent compounds on which the '808 patent is based. The '808 patent asserts, however, that the absence of the 7-hydroxy (at the para position) would lead one of ordinary skill in the art to expect that the '808 patent compounds would not work because they "lack . . . the supposedly

essential 7-hydroxy group,” (*Id.* at col. 1, ll. 46-49) and thus do not “resemble the structure of dopamine.” (*Id.* at col. 1, ll. 39-41.)

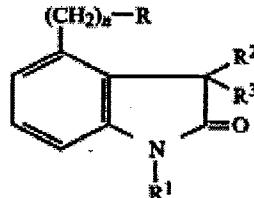
24. The ‘808 patent also states that, unlike the prior art compounds described in its own ‘944 patent, the ‘808 patent compounds do not exhibit the undesirable side effect of tachyphylaxis (*i.e.*, development of dose tolerance to the drug) when administered to patients in doses sufficient to treat cardiovascular indications, including hypertension. Specifically, the ‘808 patent states that the claimed compounds “may not be subject to tachyphylaxis … when compared with the prior art compounds based on preliminary pharmacological tests with the preferred species of this invention” (‘808 patent, col. 1, ll. 48-53) and that ropinirole hydrochloride “did not cause tachyphylaxis … as did its 7-hydroxy congener [*i.e.*, the corresponding compound disclosed in Plaintiffs’ ‘944 patent] of the prior art” in one of the *in vivo* tests performed in dogs. (‘808 patent, col. 4, ll. 50-52.)

25. All of the many different compounds covered by the ‘808 patent are distinguished over the prior art ‘944 patent with reference to these allegedly unexpected dopamine agonist properties. (808 patent, col. 4, ll. 31-34.) In support of these arguments, the ‘808 patent specification describes the results of various pharmacological tests for dopaminergic activity that were conducted using ropinirole. (*Id.* at col. 4, ll. 45-62.) These tests include: (1) the perfused rabbit ear artery test; (2) the cardioaccelerator nerve preparation in the dog; (3) the perfused hind limb preparation in the dog; (4) intravenous infusion in the DOCA-salt hypertensive rat; (5) intravenous infusion in the spontaneously hypertensive rat; (6) intravenous infusion in the renal hypertensive rat; (7) intravenous infusion in the normotensive rat; and (8) oral administration to the conscious DOCA salt hypertensive rat. (*Id.*)

26. Claim 1 of the '808 patent broadly claims all of the various compounds that share the common structure described in the specification. Claims 2-7 depend from claim 1 and further limit the scope of claim 1.

What is claimed is:

1. A compound of the structural formula:



in which:

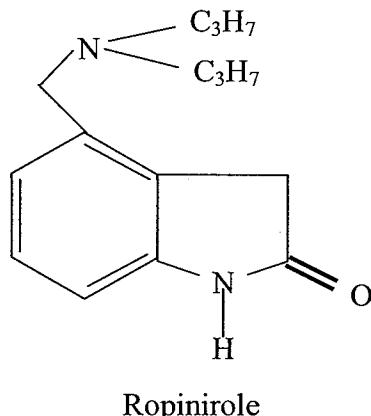
n is 1-3;

R is amino, C<sub>1-6</sub>-lower alkylamino, di-(C<sub>1-6</sub>-lower alkyl)amino, allylamino, diallylamino, N-(C<sub>1-6</sub>-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are, each, hydrogen or C<sub>1-4</sub>-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

2. The compound of claim 1 in which R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are hydrogen, n is 2 and R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino.
3. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.
4. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone as the free base.
5. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.
6. The compound of claim 1 being 4-(2-aminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.
7. The compound of claim 1 being 4-(4-hydroxyphenethylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

27. By stipulation, claim 5 is the only claim of the '808 patent that Plaintiffs assert is infringed. As shown above, claim 5 of the '808 patent is a dependent claim that incorporates by reference all of the limitations of claim 1. The compound recited in claim 5—4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride—is commonly referred to as ropinirole hydrochloride. Ropinirole hydrochloride is a pharmaceutically acceptable salt of ropinirole, the compound represented by the general structure in claim 1 of the '808 patent in which the variable n is 2, the substituent R is di-n-propylamino, and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are all hydrogen atoms. The "n-propyl" group is a "C<sub>1-6</sub> lower alkyl" having three carbons and represented by the formula C<sub>3</sub>H<sub>7</sub>. Thus, ropinirole is represented by the following structural formula:



28. In addition to the "compound" claims in the '808 patent, the '808 patent also recites claims directed to "a pharmaceutical composition having D<sub>2</sub> receptor agonist activity" that includes "a non-toxic, agonist quantity" of the various compounds described in the '808 patent. (See '808 patent, claim 8.) These D<sub>2</sub> agonist "pharmaceutical composition" claims include claims directed to the composition's pharmaceutical use as a drug for treatment of hypertension (claim 11) and a preferred dosage quantity of "50-500 mg" (claim 12).

**B. The ‘860 Patent Covers The Use Of The ‘808 Compounds To Treat Parkinson’s Disease**

29. The ‘860 patent is entitled “Treatment of Parkinson’s Disease.” It was filed on May 19, 1988, and claims priority from United Kingdom Application No. 8712073, which was filed on May 21, 1987. The ‘860 patent names Dr. David A. A. Owen as its sole inventor. Dr. Owen was a pharmacologist at GSK.

30. The ‘860 patent is directed to the use of a series of D<sub>2</sub> dopamine agonist compounds, some of which—including ropinirole hydrochloride—are covered by the claims of the ‘808 patent, to treat Parkinson’s disease. The ‘860 patent also covers the use of many of the compounds described in the ‘944 patent. Both the ‘944 and ‘808 patents are prior art to the ‘860 patent.

31. The ‘860 patent acknowledges that ropinirole hydrochloride and the other claimed compounds were known in the prior art as D<sub>2</sub> dopamine agonists that could be used to treat cardiovascular conditions. The ‘860 patent further acknowledges that other dopamine agonist compounds that were active at post-synaptic D<sub>2</sub> receptors were known to be effective in treating Parkinson’s disease. (‘860 patent, col. 1, ll. 36-38: “An alternative form of therapy is to administer post-synaptic dopamine agonists, for example ergot alkaloids such as bromocriptine ....”) The ‘860 patent purports to distinguish this prior art by implying that a person of ordinary skill in the art would only have understood that the ‘808 and ‘944 patent compounds acted on *pre-synaptic* D<sub>2</sub> receptors, and therefore would not have understood that the claimed compounds are also active at *post-synaptic* D<sub>2</sub> receptors or that the claimed compounds could have been used to treat Parkinson’s disease. (‘860 patent, col. 1, ll. 48-58.)

32. To distinguish other prior art D<sub>2</sub> agonists, the ‘860 patent cites a paper authored by the ‘808 patent’s inventor Mr. Gallagher and other researchers employed by GSK as finding

that the compounds described in the '808 patent are "not [] capable of producing the central behavioural effects often seen with dopamine agonists." ('860 patent, col. 1, ll. 54-58.)

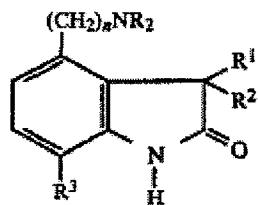
33. In support of the anti-Parkinson's effects of the compounds claimed in the '860 patent, the '860 patent specification describes various tests run on animals for potential anti-Parkinson's activity. ('860 patent, col. 3, l. 41-col. 6, l. 65.) These included testing for: (1) spontaneous locomotor activity in mice; (2) locomotor activity in rats; (3) and anti-Parkinson activity in MPTP-treated marmosets. (*Id.* at col. 4, ll. 1-23; col. 4, l. 40-col. 5, l. 6; col. 5, l. 45-col. 6, l. 33.)

34. The specification of the '860 patent only explicitly describes how to use one of these compounds—ropinirole hydrochloride—to treat patients with Parkinson's disease. The specification identifies no clinical studies or other tests that were conducted on humans.

35. Claim 1 of the '860 patent broadly claims the use of all of the various compounds that share the common structure described in the specification for treatment of the Parkinson's disease in humans. Indeed, given the various possible combinations of functional groups that can be substituted at the R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> positions and the length of the side chain (as determined by the value of n), claim 1 of the '860 patent literally covers 750 different compounds.

What is claimed is:

1. A method of treatment of Parkinson's disease which comprises administering an effective non-toxic amount for the treatment of Parkinson's disease of a compound of the following structure:



in which each group R is hydrogen or C<sub>1-4</sub> alkyl;

R<sup>1</sup> and R<sup>2</sup> are each hydrogen or C<sub>1-4</sub> alkyl;

R<sup>3</sup> is hydrogen or hydroxy; and

n is 1 to 3;

or a pharmaceutically acceptable salt thereof to a subject in need thereof.

36. Claims 2 and 3 claim the use of specific compounds for treatment of Parkinson's disease.

What is claimed is:

2. A method of treatment of Parkinson's disease which comprises administering an effective non-toxic amount for the treatment of Parkinson's disease of 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone to a subject in need thereof.

3. A method of treatment of Parkinson's disease which comprises administering an effective non-toxic amount for the treatment of Parkinson's disease of 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride to a subject in need thereof.

37. By stipulation, claim 3, shown above, is the only claim of the '860 patent that Plaintiffs assert is infringed by Teva's filing of its ANDA. Claim 3 is specifically directed to the use of ropinirole hydrochloride to treat Parkinson's disease.

V. [REDACTED]

38. Both the '808 and '860 patents' specifications describe hundreds of different compounds with expected pharmacological properties based on various tests conducted on a single compound—ropinirole hydrochloride. Based on these specifications, the patents assert rights over hundreds of different compounds with expected D<sub>2</sub> agonist properties. Each of these patents identifies a single person as the inventor of this subject matter. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A.

Mr. Gallagher is the sole named inventor of the '808 patent.





B.

Dr. Owen is the sole named inventor of the '860 patent.



## **CONCLUSIONS OF LAW AND UNDERLYING FACTS**

### **VI. LEGAL STANDARDS FOR PATENT INVALIDITY**

50. A claimed invention can be invalid as anticipated or obvious. *See* 35 U.S.C. §§ 102, 103(a). Although a patent is presumed valid under 35 U.S.C. § 282, where the party challenging validity of the patent relies on prior art or other evidence that was not considered by the USPTO, there is “*no reason to defer to the PTO.*” *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (emphasis in original).

#### **A. Priority and Definition of Prior Art**

51. Prior art is what was known before as defined in 35 U.S.C. § 102, and includes United States and foreign patents and printed publications that were patented or published before the invention by the applicant for patent or more than one year prior to the date of the application for patent in the United States. *See In re Wertheim*, 646 F.2d 527, 532 (C.C.P.A. 1981); 35 U.S.C. § 102. For purposes of § 102(f), prior art need not be publicly available but only known to the named inventor. *OddzOn Prods. Inc. v. Just Toys Inc*, 122 F.3d 1396, 1401-03 (Fed. Cir. 1997); 35 U.S.C. § 102(f).

52. The date of invention is presumed to be date of filing of the application for patent, unless an earlier date of conception is proven. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576-77 (Fed. Cir. 1996). Corroboration is required where a party seeks to show an earlier date of conception through the oral testimony of an inventor. *Id.* at 1577.

53. “[T]he person who first conceives, and, in a mental sense, first invents... may date his patentable invention back to the time of its conception, if he connects the conception with its reduction to practice by reasonable diligence on his part, so that they are substantially one continuous act.” *Id.* (internal quotations omitted). “Conception is the ‘formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is

hereafter to be applied in practice.”” *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). “Conception requires both the idea of the invention’s structure and possession of an operative method of making it.” *Id.*

#### **B. Anticipation**

54. A claimed invention is invalid as anticipated if a single prior art reference published more than one year before the date the patent application was filed discloses each and every limitation set forth in a claim, either expressly or inherently. 35 U.S.C. § 102(b); *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997); *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

55. When the claimed invention “reads on” a prior art reference, the invention is said to be anticipated by that reference, and any claim purporting to patent the invention is deemed invalid. *See Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999) (citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985)).

56. “Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates . . . the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co.*, 190 F.3d at 1347.

57. Newly discovered results of known processes directed to the same purpose are inherent and unpatentable. *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (citing *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978)). Whether a person ordinarily skilled in the art would have recognized the inherent characteristics of the functioning of the prior art is irrelevant, if those inherent characteristics indeed exist. *See Atlas Powder*, 190 F.3d at 1349 (“Insufficient prior understanding of the inherent properties of a

known composition does not defeat a finding of anticipation.”) (citing *Titanium Metals*, 778 F.2d at 782).

58. To anticipate, a printed publication must also be enabling. *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

59. The inherent effects or results of a process or method disclosed in a reference may be proven by extrinsic evidence, including disclosures after the priority date of the patent. *Bristol-Myers*, 246 F.3d at 1379-80 (noting that enablement of an anticipatory reference may be shown by later references).

60. Reliance on extrinsic evidence is sometimes appropriate to explain the meaning of terminology in a prior-art reference raised under § 102, *see Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), or to explain how such a prior-art reference discloses the enablement of an alleged invention, *see In re Donohue*, 766 F.2d at 533.

### C. Obviousness

61. A claimed invention is invalid due to obviousness if the differences between it and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art.” 35 U.S.C. § 103(a); *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 13-14 (1966)).

62. The obviousness inquiry is a question of law based on certain factual inquiries, including: (1) “the scope and content of the prior art”; (2) “the level of ordinary skill in the field of the invention”; (3) “the differences between the claimed invention and the prior art”; and (4) secondary, objective considerations of nonobviousness including long-felt need, commercial success, the failure of others, or unexpected results. *SIBIA Neurosciences, Inc. v. Cadus Pharm.*

*Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000) (citing *Graham*, 383 U.S. at 17-18); *see Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984).

63. The scope of the prior art includes art that is “reasonably pertinent to the particular problem with which the inventor was involved,” *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535 (Fed. Cir. 1983) (internal quotes omitted), and can include (1) knowledge or use by others in the United States before the invention by the applicant for patent, and (2) United States and foreign patents and printed publications that were patented or published before the invention by the applicant for patent or more than one year prior to the date of the application for patent in the United States. 35 U.S.C. §§ 102(a), (b).

64. Some “teaching, suggestion, or reason” to combine references is required. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579 (Fed. Cir. 1997). Whether a motivation to combine prior art references has been demonstrated is a question of fact. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1348 (Fed. Cir. 2000).

65. The motivation to combine may be found either explicitly or implicitly: (1) in individual prior-art references or in prior art references as a whole; (2) in the knowledge of those of ordinary skill in the art; or (3) from the nature of the problem to be solved. *See Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (Fed. Cir. 2006) (finding that no “actual teaching to combine [is required] to conclud[e] that one of ordinary skill in the art would know to combine references” and that “motivation to combine need not be found in prior art references, but can equally be found in the knowledge generally available to one of ordinary skill in the art such as knowledge of a problem to be solved”); *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996); *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461,

1472 (Fed. Cir. 1997) (finding that “there is no requirement that prior art [references] contain an express [motivation or] suggestion to combine”).

66. “The test for an implicit showing [of motivation to combine the relevant prior art teachings] is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.” *Alza Corp.*, 464 F.3d at 1290-91 (quoting *In re Kahn*, 441 F.3d at 987-88).

67. If a reference “teaches away” from a given combination, it may negate a motivation to modify the prior art to meet the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1308 (Fed. Cir. 2006) (citing *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006)). But to show that a references teaches away from a given combination, the patentee must show that “a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *Id.*

68. Whether the claimed invention is obvious must be evaluated “from the vantage-point of a hypothetical person having ordinary skill in the art to which the patent pertains” and requires a factual determination of the level of ordinary skill in the art. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998); *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 716 (Fed. Cir. 1991).

69. The hypothetical person of ordinary skill in the art is presumed to be aware of all prior art in the same or analogous fields. *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991). The level of ordinary skill in the art may be found by inquiring into: (1) the “type of problems encountered in the art; [(2)] prior art solutions to those problems; [(3) the] rapidity with which innovations are made; [(4) the] sophistication of the technology; and [(5) the] education[] level

of active workers in the field.” *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). “Although the educational level of the inventor may be a factor to consider in determining the level of ordinary skill in the art, it is by no means conclusive.” *Orthopedic Equip. Co.*, 707 F.2d at 1382 (affirming a district court holding that one of ordinary skill in the art had additional education that the inventor did not). All of these factors may not be present in every case, and one or more of them may predominate. *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 696 (Fed. Cir. 1983).

70. Expert testimony is pertinent to an evaluation of the level of ordinary skill in the art at the time of the invention and knowledge that a person of ordinary skill in the art would have possessed at the time of the invention. *Alza Corp.*, 464 F.3d at 1294; *see Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376, 1382 (Fed. Cir. 1983).

71. In assessing motivation to combine prior art teachings, “a court must ask ‘whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims.’” *Alza Corp.*, 464 F.3d at 1290 (quoting *In re Kahn*, 441 F.3d at 988).

72. The inspiration to combine prior art references must also offer a “reasonable expectation of success.” *In re O’Farrell*, 853 F.2d 894, 904 (Fed. Cir. 1988). Absolute certainty is not necessary to establish a reasonable expectation of success. *Id.* at 903-04. The presence or absence of a “reasonable expectation of success” is a question of fact. *Medichem, S.A.*, 437 F.3d at 1165.

73. Evidence of secondary considerations of nonobviousness “is only significant if there is a nexus between the claimed invention” and the particular secondary consideration of

nonobviousness. *Ormco Corp.*, 463 F.3d at 1311-12; *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984) (“A nexus between the merits of the claimed invention and the evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision.”).

74. Commercial success is relevant only if it flows from the merits of the claimed invention. *See, e.g., In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (holding that even assuming that a party has sufficiently demonstrated commercial success, “that success is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter.”); *Ormco Corp.*, 463 F.3d at 1311-12. “Thus, if the commercial success is due to an unclaimed feature of the device, the commercial success is irrelevant.” *Id.* at 1312. “So too if the feature that creates the commercial success was known in the prior art, the success is not pertinent.” *Id.* In addition, evidence that the success of a product was based on significant marketing and advertising “obscur[es] any nexus that might have existed between the merits of the product and its commercial success.” *See McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003).

## VII. CLAIM 5 OF THE ‘808 PATENT IS INVALID FOR OBVIOUSNESS

### A. Field Of The ‘808 Patent Is Structure-Activity Relationships For Developing Dopamine Agonist Compounds

75. The ‘808 patent is directed to structure-activity relationships for dopamine agonists. The ‘808 patent describes and claims more than one thousand compounds that act as dopamine agonists. These compounds are related in that they have a common structural backbone, shown in claim 1 of the ‘808 patent, thus the knowledge of structure-activity relationships is a necessary prerequisite to understanding the ‘808 patent.

76. The ‘808 patent distinguishes its claimed compounds from the prior art with reference to structure-activity relationships. In particular, it distinguishes the claimed compounds from the dopamine agonist compounds described in the prior art ‘944 patent with reference to a single different structural relationship—*i.e.*, the compounds claimed in the ‘808 patent lack a hydroxy (OH) group in position 7 (the “para” position relative to the aminoethyl side chain). (‘808 patent, col. 1, ll. 46-48: “The indolone compounds of this invention have beneficial cardiovascular activity despite the lack of the supposedly essential 7-hydroxy group.”) The ‘808 patent tells the reader that this change is significant because “[o]ne skilled in the structure function art will appreciate that … [w]ithout this key group [*i.e.*, the 7-hydroxy group], the resulting compounds would not be expected to have cardiovascular activity.” (‘808 patent, col. 1, ll. 38-43.)

77. The ‘808 patent also requires an understanding of the pharmacology of dopamine agonists. The ‘808 patent specification describes various tests for D<sub>2</sub> dopaminergic activity and expected pharmacological uses of the claimed compounds. Moreover, claims 8-12 of the ‘808 patent claim the pharmaceutical use of the many different compounds covered by the ‘808 patent, including their use as cardiovascular agents based on their predicted D<sub>2</sub> agonist properties. The predictability of the dopaminergic activity and cardiovascular effects (or lack thereof) of these many different variations can be derived from structure-activity relationships applied to the backbone structure.

78. Because the ‘808 patent includes both of these sets of claims and explicitly is directed to those knowledgeable in the “structure function art,” the ‘808 patent requires an understanding of both structure-activity relationships for dopamine agonist molecules and their expected pharmacological activity.

**B. Level Of Ordinary Skill In The Art Of The '808 Patent**

79. Given the field of the patent, one skilled in the art of this field would likely have a graduate degree in medicinal chemistry with knowledge of the biology of dopamine agonists, *i.e.*, the expected pharmacology from the changes made to the structures of the molecule. One skilled in the field could also be a pharmacologist, likely with a graduate degree, with knowledge of the medicinal chemistry aspects of dopamine agonist structures.

**C. Date of Invention for Purposes of Prior Art**

80. The date of invention of the claims of the '808 patent is December 7, 1982. Accordingly, any reference published or patent issued anywhere in the world prior to December 7, 1982 is considered prior art with respect to the '808 patent claims under 35 U.S.C. § 102(a), and any patent issued from a patent application filed before December 7, 1982 is considered prior art under 35 U.S.C. § 102(e). Separately, regardless of the date of invention of the claims of the '808 patent, any reference published or patent issued anywhere in the world prior to December 7, 1981 constitutes prior art under 35 U.S.C. § 102(b).<sup>1</sup>

**D. Claim 5 Is Obvious In View Of The '944 Patent And The Prior Art Showing The "Supposedly Essential 7-Hydroxy" Was Not Essential.**

81. The '808 patent states that the compounds claimed therein are distinguishable from dopamine agonists described in GSK's own prior art '944 patent as having cardiovascular

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<sup>1</sup> The date of invention of claim 5 of the '808 patent is its filing date—December 7, 1982. [REDACTED]

effects because the compounds claimed in the '808 patent, including ropinirole, have a 7-hydroxy group that is analogous to the para-hydroxy group of dopamine. According to the '808 patent, prior to the discovery of the invention claimed in the '808 patent, those of ordinary skill in the art would have believed that the para-hydroxy group in these known indolone compounds was "key" to their having dopamine agonist activity and corresponding cardiovascular effects:

4-Aminoalkyl-7-hydroxy-2(3H)-indolones are described in U.S. Pat. No. 4,314,944 to have a beneficial effect on abnormal conditions of the cardiovascular system. More specifically, such compounds are said to have a vasodilatation effect on the kidney which is similar to that of dopamine, thereby inducing anti-hypertensive activity due to a dopaminergic mechanism.

The basic structure of the prior art compounds is similar to that of the well known cardiovascular agent they mimic, dopamine: [structures omitted]

One skilled in the structure function art will appreciate that the 7-hydroxy group of the compounds of the prior art is necessary for them to resemble the structure of dopamine. *Without this key group, the resulting compounds would not be expected to have cardiovascular activity.*

('808 patent, col. 1, ll. 9-43 (emphasis added).) The '808 patent then describes the discovery of the dopaminergic activity and "beneficial cardiovascular activity" of ropinirole and the other claimed compounds "despite the[ir] lack of the supposedly essential 7-hydroxy group" as surprising. (*Id.* at col. 1, ll. 46-48.)

82. As discussed below, the prior art proffered by the parties shows that the para-hydroxy group of dopamine and the corresponding 7-hydroxy group of these prior indolone compounds was, in fact, known to not be essential to their dopaminergic activity and effects in the peripheral system. As a result, the removal of the 7-hydroxy group from these prior art compounds to get ropinirole or other compounds claimed in the '808 patent was an obvious variation on what was known in the prior art and claim 5 of the '808 patent is invalid for the reasons discussed below.

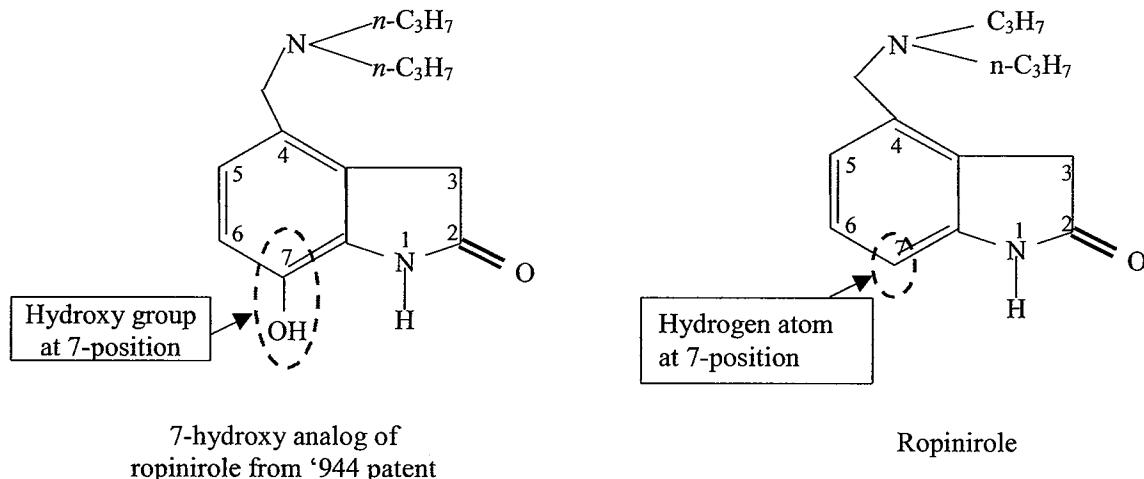
**1. The Scope And Content Of The Prior Art And The Differences From Claim 5.**

83. One of the closest prior art references to the '808 patent is GSK's own '944 patent. As described above, the '944 patent is the patent upon which the '808 patent was alleged to be an improvement. The '944 patent constitutes prior art to the '808 patent under 35 U.S.C. § 102(a), since the '944 patent issued on February 9, 1982, before the date of invention of the '808 patent—December 7, 1982. Alternatively, the '944 patent is prior art under 35 U.S.C. § 102(e), because the patent application from which the '944 patent issued was filed prior to the date of invention of claim 5 of the '808 patent.

84. Claim 5 of the '808 patent differs from the preferred embodiment of the prior art compounds claimed in the '944 patent in only one way: ropinirole hydrochloride lacks a hydroxy group in position 7 that is present in the preferred compound of the '944 patent.<sup>2</sup> Thus, claim 5 is invalid for obviousness if it would have been obvious to one skilled in the art at the time of the '808 patent invention to have removed the 7-hydroxy group from the preferred compound of the '944 patent.

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<sup>2</sup> That claim 5 recites ropinirole in its hydrochloride salt form makes no difference to the obviousness analysis. Drug compounds are typically used in salt form and pharmaceutically acceptable salts for compounds of the type described in the '808 patent are commonly known in the field of art. For example, the '944 patent describes the use of hydrochloride salts with these types of compounds. ('944 patent, col. 1, ll. 58-68.) Moreover, the prior art '944 patent identifies exemplary compounds "Dopamine B" and "Dopamine D" that are hydrochloride salts. ('944 patent, col. 4, ll. 32-39.) The selection of a particular salt compound is usually a matter of manufacturing convenience, because the salt typically dissociates shortly after administration to a patient into the active ion (for claim 5, ropinirole) and an anion (for claim 5, chloride) such that the particular salt form selected has little effect on the activity of the active ingredient in the body. Because the use of a salt form of the active ingredient was well-known in the prior art of record, the naming of the hydrochloride salt in claim 5 adds nothing novel to the alleged invention, and for purposes of this analysis, a prior art reference or combination of prior art references that renders the active ingredient ropinirole obvious also renders the salt compound ropinirole hydrochloride obvious.

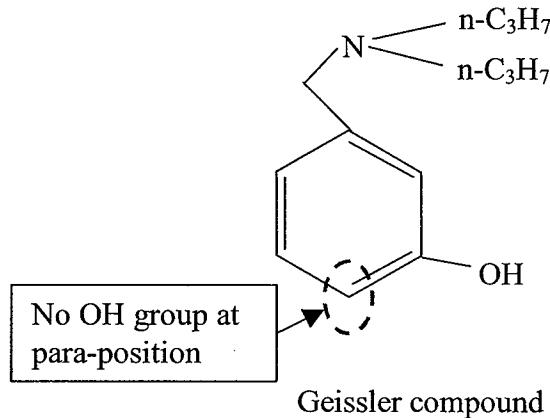


85. At least four prior art references demonstrate that it was well-known in the field of structure-activity relationships for dopaminergic compounds that, contrary to the statement in the '808 patent, the 7- or para-hydroxy was not essential or necessary for dopaminergic action.

86. Cannon, J.G., "*Dopamine Congeners Derived from Benzo(f) quinoline Ring*," *Advances in Biosciences*, 1979, Vol. 20: 87-94 ("Cannon 1979 Article") shows an ergoline dopamine agonist that had been demonstrated to have D<sub>2</sub> agonist activity even though it lacked the para- or 7-hydroxy. The article explains that it is the hydroxy group in the *meta*-position—not the *para*-position—that is highly important for dopaminergic activity. (Cannon 1979 Article at 92.) The article further explains that D<sub>2</sub> agonist compounds can nonetheless be made without the *meta*-hydroxy as long as some "bioisosteric" group is substituted for it. (*Id.*) One skilled in the structure function art for dopaminergic agents would recognize from the Cannon 1979 Article that a para-hydroxy is not necessary for D<sub>2</sub> dopaminergic action. The Cannon 1979 Article constitutes prior art to claim 5 of the '808 patent under 35 U.S.C. § 102(b), because it was published more than a year before the application for the '808 patent was filed.

87. Geissler, H., *3-[2-(Dipropylamino)ethyl]phenol: a new and selective dopaminergic agonist*, *Arch. Pharm. (Weinheim)* Vol. 310: 749-756 (1977) ("Geissler article")

discloses the dopamine agonist 3-[(2-dipropylamino)ethyl]phenol (also referred to as “N,N-di-n-propyl-*m*-tyramine”), which can be represented by the formula below:



The Geissler compound was both expected (Geissler Article at 749) and shown to have dopaminergic D<sub>2</sub> activity (*id.* at 755), both centrally and peripherally, even though it lacked a para-OH group. In particular, the Geissler compound with no para-hydroxy group was shown to be a “direct” (*i.e.*, post-synaptic) central D<sub>2</sub> agonist. (*Id.*) The Geissler Article constitutes prior art to claim 5 of the ‘808 patent under 35 U.S.C. § 102(b), because it was published more than a year before the application for the ‘808 patent was filed.

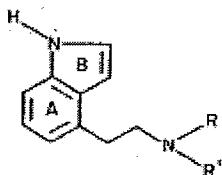
88. Sumners, C., Dijkstra, D., de Vries, J., and Horn, A., *Neurochemical and Behavioural Profiles of Five Dopamine Analogues*, Naunyn-Schmiedeberg’s Arch. Pharmacol. 316:304-310 (1981) (“Sumners Article”), provides data to directly compare the dopamine agonist characteristics of the Geissler compound and the corresponding compound having a para-hydroxy group—dipropyl dopamine. The Geissler compound, which lacks the para-hydroxy group that the ‘808 patent characterizes as “essential” to dopaminergic activity, was shown to be “4 times more potent in decreasing striatal HVA” than the corresponding compound with the para-hydroxy group. (Sumners Article at 308.) The Sumners Article describes a compound’s ability to decrease striatal HVA as “indicating dopamine agonist activity.” The Sumners Article

constitutes prior art to claim 5 of the '808 patent under 35 U.S.C. § 102(b) because it was published more than one year before the application for the '808 patent was filed.

89. The Sumners Article also generally describes the authors' efforts to determine whether the para-hydroxy group of dopamine and various dopaminergic compounds was essential to their dopamine agonist activity. For example, the Sumners Article describes monopropyl-monophenethyl-m-tyramine (compound e) as a potent central and peripheral dopaminergic agonist that induced stereotypy (*i.e.*, CNS effects) in rats. (Sumners Article at 308.) Compound e retains the meta-hydroxy group of dopamine (analogous to the NH group at position 1 in the pyrrole ring of ropinirole and the prior art 7-hydroxy analog described in the '944 patent), it does not include the para-hydroxy group, which would correspond to the 7-hydroxy group in the analog described in the '944 patent. Moreover, compound e is described as acting upon pre-synaptic D<sub>2</sub> receptors. Overall, the Sumners Article taught those of ordinary skill in the art that "the monohydroxylated dopamine analogues tested [*i.e.*, those lacking a *para*-hydroxy group] were potent dopamine agonists as far as dopamine metabolism and stereotypy," *i.e.*, a CNS effect "thought to be due to the interaction of the agonist at postsynaptic dopamine receptors (Ernst 1967)." (*Id.* at 308-09.) The results reported in the Sumners Article taught a person of ordinary skill in the art that, contrary to the statement in the '808 patent specification, it was not essential for a compound to have the para-hydroxy group of dopamine (or some bioisosteric group) in order for the compound to act as a D<sub>2</sub> agonist.

90. Cannon, J.G., Demopoulos, B.J., Long, J.P., Flynn J.R. and Sharabi, F.M., *Proposed Dopaminergic Pharmacophore of Lergotrile, Pergolide, and Related Ergot Alkaloid Derivatives*, J. Med. Chem. - Communications to the Editor, 24: 238-240 (1981) ("Cannon 1981 article") describes a compound (compound 9) that is structurally identical to ropinirole in all

respects except that it includes a double bond between the carbon atoms in positions 2 and 3 to form what is called an “indole” ring system, rather than a double-bonded oxygen attached to the carbon at position 2 in what is called an “indolone” ring system.



Compound 9

91. The Cannon 1981 *Article* demonstrated that compound 9 had D<sub>2</sub> agonist activity even though it lacked the supposedly “essential” para-hydroxy group of dopamine. This led the authors to suggest that compound 9 was a “pharmacophore,” *i.e.*, a set of structural features in a molecule that is recognized at a receptor site and is responsible for a compound’s biological activity, of several known dopamine agonist ergot derivatives then used to Parkinson’s disease:

The biological data presented in this communication suggest that [compound] 9 (R=R’=n-C<sub>3</sub>H<sub>7</sub>) is a dopamine agonist. In the anesthetized cat, lergotrile (1) and [compound] 9 are quite parallel in their actions and potencies. The data are consistent with the proposal that the structure of [compound] 9 is the active pharmacophore in the lergotrile and pergolide molecules.

(*Id.* at 240.)

92. Later research by Drs. Cannon and Long—reported in Cannon, J.G., Lee, T., Ilhan, M., Koons, J. and Long, J.P., *6-Hydroxy-4-[2-(di-n-propylamino)ethyl]indole: Synthesis and Dopaminergic Actions*, J. Med. Chem. 27:386-89 (1984) (“Cannon 1984 Article”)—suggested that the D<sub>2</sub> agonist activity of compound 9 resulted from the formation of an active metabolite *in vivo* that added another *meta*-hydroxy group in position 6, but similarly lacked the supposedly essential para-hydroxy group in position 7. (Cannon 1984 Article at 386.) Notably, lergotrile—one of the ergot derivatives that was known to work as a central D<sub>2</sub> dopamine

agonist—was believed to be similarly metabolically activated by the addition of a meta-hydroxy group. (*Id.*)

**2. The Subject Matter Of Claim 5 Would Have Been Obvious In View Of The ‘944 Patent And The Prior Art**

93. As discussed above, the evidence that the 7-hydroxy group was not essential for D<sub>2</sub> activity—contrary to the statements in the ‘808 patent—is overwhelming. It would have been obvious to one skilled in the art to remove the 7-hydroxy group from the preferred compound disclosed in the ‘944 patent as an obvious variant on the ‘944 compound, since the prior art already demonstrated that removing the para-hydroxy group in other series of dopamine agonist compounds resulted in compounds that are potent dopamine agonists. Indeed, in the Sumners Article (at 308), which focused on the effect of removing the para-hydroxy group, a compound lacking the para-hydroxy group was found to be four times more potent than its analog with a para-hydroxy group. Based on this prior art, a person of ordinary skill in the art would have had a reasonable expectation that removing the 7-hydroxy group from the preferred compound (to yield ropinirole) would have resulted in a dopamine agonist compound.

94. The possibility of obtaining a more potent dopamine agonist would not be the sole motivation for a person of ordinary skill in the art to modify the preferred compound of the ‘944 patent by removing its para-hydroxy group. One skilled in the art would also be motivated to remove the 7-hydroxy group from the preferred compound of the ‘944 patent, because that modification would be expected to make the molecule more lipophilic, and thus more likely both to be absorbed into the bloodstream after oral administration—the generally preferred route of administration for drugs used to treat chronic conditions like Parkinson’s disease.

95. One of ordinary skill in the art would not have been dissuaded from removing the 7-hydroxy group from the compounds of the ‘944 patent by the possibility that the indole

compound 9 of the Cannon 1981 Article was not itself dopaminergically active and was instead metabolically activated *in vivo* (*i.e.*, in the body) by the addition of a meta-hydroxy group. Lergotrile, a compound known in the prior art to be dopaminergically active and commercially used in treating Parkinson's disease prior to December 7, 1982, was believed to be metabolically activated in a similar fashion. (Cannon 1984 Article at 386.)

**E. Claim 5 Is Invalid As Obvious In Light Of The 1981 Cannon Article And The Prior Art Teaching The Use Of Indolone Ring Systems**

96. As described above, the Cannon 1981 Article differs from claim 5 only by its use of an indole, rather than an indolone ring system. In other words, the indole compound disclosed in the prior art Cannon 1981 Article has a double bond between the carbon atoms at positions 2 and 3, while ropinirole has a carbon-oxygen double bond at position 2.

97. One skilled in the field of structure-activity relationships for dopamine agonists would recognize that an indolone system is an obvious variant from the indole ring system used in the Cannon 1981 Article. Both the indole and indolene structures include a bioisosteric group to substitute for the highly important meta-hydroxy group that is necessary to retain the dopaminergic activity of a compound. (Cannon 1979 Article at 92.) The Cannon 1981 Article teaches that the NH group in position 1 (within the pyrrole ring) of indole compound 9 from the Cannon 1981 Article was bioisosteric with the meta-hydroxy group of dopamine. (Cannon 1981 Article at 238 (citing Cannon 1979 Article).) The indolone compound ropinirole (as well as the other indolone compounds covered in the broader claims of the '808 patent) includes the same bioisosteric NH group at position 1. In prior art compound 9 from the Cannon 1981 Article, the hydrogen atom in the NH group is kept available for binding with the D<sub>2</sub> receptor by the double bond between the carbon atoms at positions 2 and 3. A person of ordinary skill in the structure function art would have understood that a carbon-oxygen double bond at position 2, like that

present in ropinirole and the other compounds claimed in the '808 patent, could be used to accomplish the same effect. Thus, a person of ordinary skill in the art would have reasonably expected that modifying the indole compound 9 from the Cannon 1981 Article to form an indolone would have resulted in a D<sub>2</sub> agonist compound.

98. To the extent that substitution of indolone for indole would not have been readily obvious to one skilled in the structure function art solely based on the knowledge in the art about these ring systems and their chemical properties, it would have been in light of the prior art '944 patent. The '944 patent teaches D<sub>2</sub> agonist indolone compounds. Its teachings would have motivated a person of ordinary skill in the art to convert the indole compound 9 from the Cannon 1981 Article into an almost structurally identical indolone to yield ropinirole as claimed in the '808 patent.

99. The '944 patent unquestionably shows the active dopamine agonist properties of indolones as dopaminergic agents and describes dopaminergically-active indolone compounds as having the same profile of cardiovascular effects as is ascribed to the compounds claimed in the '808 patent, including ropinirole. The compounds disclosed in the '944 patent are described as having "a beneficial effect on abnormal cardiovascular conditions especially on the kidney by means of increasing renal blood flow and decreasing renal vascular resistance. Bradycardia is also observed." ('944 patent, col. 3, ll. 61-65.)

"The method of producing improvement in abnormal cardiovascular conditions by inducing renal vasodilatation, antihypertensive effects and bradycardia activity in accordance with this invention comprises administering ...a compound of Formula I or a pharmaceutically acceptable salt thereof."

('944 patent, col. 5, ll. 47-53.) It would have been obvious to one skilled in the field of the '808 patent to have modified the indole compound 9 of the Cannon 1981 Article to an indolone to yield ropinirole in light of the '944 patent.

**F. The Secondary Considerations Of Non-Obviousness Do Not Reflect Non-Obviousness Of The '808 Patent**

100. No secondary considerations of non-obviousness change the conclusion that claim 5 of the '808 patent is obvious in view of the prior art.

101. GSK alleges copying supports the non-obviousness of the '808 patent. Copying, however, is not probative of non-obviousness in an ANDA case. *Eli Lilly & Co. v. Teva Pharmas. USA, Inc.*, 2004 WL 1724632, at n.21 (S.D. Ind. July 29, 2004) ("[B]ecause the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects . . . demonstration of equivalency of [a generic version of a drug] to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention."). In any case, the evidence shows that Teva did not copy the '808 patent or the Requip drug product other than the necessary including of the same active ingredient ropinirole hydrochloride for its ANDA.

102. GSK alleges that the alleged commercial success of its Requip drug product supports the non-obviousness of the '808 patent. However, any alleged commercial success enjoyed by Requip does not demonstrate non-obviousness of the '808 patent on the facts of this case. For example, the '808 patent discusses the cardiovascular applications of the claimed compounds. Ropinirole has never been sold for cardiovascular indications.

103. Further, Requip has not been highly commercially successful in the marketplace *vis-à-vis* its competition. To the extent it has enjoyed commercial success, this success is due to external factors, rather than from the claimed features of the patented invention. These external factors include: (1) massive efforts and funds spent on marketing, advertising, promoting, and selling the product; (2) Requip's FDA approval for treatment of Restless Legs Syndrome ("RLS"), which makes it more likely that physicians will prescribe Requip over other similarly effective drugs; and (3) GSK's 8 Week Requip starter kit, which provides 8 weeks of free

samples and detailed directions to counteract Requip's long and laborious titration schedule, an inherent disadvantage of the compound for the treatment of Parkinson's disease.

104. GSK argues the invention of claim 5 has "unexpected properties" that demonstrate that the claim is not obvious in view of the prior art. As discussed above, however, the '808 patent's assertion that those skilled in the field believed the 7-hydroxy group of the indolone compounds disclosed in the prior art '944 patent was necessary for D<sub>2</sub> agonist activity was factually wrong. Whether the inventor(s) knew it or not, those skilled in the field already knew this statement was not true, and the dopaminergic effect of ropinirole was not "unexpected." [REDACTED]

[REDACTED]. Therefore, this secondary factor also does not support a finding of nonobviousness.

105. GSK also argues that claim 5 of the '808 patent was not obvious because ropinirole solved a long-felt need that would have been addressed earlier if the invention was truly ascertainable from what was previously known in the art. That assertion is disproven because, while ropinirole is useful in treating Parkinson's disease and Restless Legs Syndrome, it is no more useful than its competitors. Significantly, ropinirole was neither the first dopamine agonist drug nor the first Parkinson's treatment. In fact, far from solving an unmet need, the need for effective Parkinson's treatments, or more significantly cures, continues. Notably, ropinirole is not approved as a treatment for any of the cardiovascular conditions discussed in the '808 patent specification. Therefore, the secondary factor of "long-felt but unresolved need" does not weigh in favor of finding claim 5 of the '808 patent nonobvious.

**VIII. CLAIM 3 OF THE '860 PATENT IS INVALID AS ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '808 PATENT AND OTHER PRIOR ART**

**A. Field Of The '860 Patent Is Pharmacology Of D<sub>2</sub> Dopamine Agonists**

106. The '860 patent is directed to the use of a number of structurally related D<sub>2</sub> dopamine agonist compounds (*i.e.*, ropinirole hydrochloride and other similar compounds) to treat Parkinson's disease. The patent specification describes various tests for D<sub>2</sub> agonist activity and Parkinson's disease. The background section of the patent describes prior art D<sub>2</sub> agonist compounds used for Parkinson's disease. As a result, the '860 patent requires an understanding of the expected pharmacological activity of D<sub>2</sub> dopamine agonist molecules.

**B. Level of Ordinary Skill In The Art Of The '860 Patent**

107. The patent at issue in this litigation is properly directed to and evaluated from the perspective of one skilled in the art. The '860 patent is directed to persons skilled in medicinal or pharmaceutical chemistry, pharmacology, neurology, or a related field, who likely have a graduate degree in at least one of these fields, and have experience researching the pharmacological effects of pharmaceutical compounds that are structurally similar to dopamine in both the CNS and peripheral nervous system.

**C. Assertion Of "Unexpected" Central D<sub>2</sub> Activity In The '860 Patent Is Based On Scientifically Improper and Misinterpreted Tests**

108. Central to consideration of the obviousness of claim 3 of the '860 patent is the patent's assertion that ropinirole and the other claimed compounds would be expected to act differently than other D<sub>2</sub> agonists. The patent acknowledges that (1) ropinirole hydrochloride and the other claimed compounds were known in the prior art as D<sub>2</sub> dopamine agonists that could be used to treat cardiovascular conditions; and (2) dopamine agonist compounds that were active at post-synaptic D<sub>2</sub> receptors were known to be effective in treating Parkinson's disease. The '860 patent seeks to distinguish the conclusion that ropinirole would simply work like other D<sub>2</sub>

agonists by citing a paper written by various GSK researchers, including the '808 patent inventor. ('860 patent, col. 1, ll. 54-58.) *See Gallagher et al., 4-[2-(Di-n-propylamino)ethyl]-2(3H)-indolone: Prejunctional Dopamine Receptor Agonist, J. Med. Chem. 28:1533-1536 (1985)* ("Gallagher Article"). This article is cited in the '860 patent for the proposition that ropinirole was not believed to have any effects in the CNS. (*Id.*)

109. The Gallagher Article's conclusion is factually flawed and one skilled in the field of the '860 patent—and thus knowledgeable about D<sub>2</sub> agonists' pharmacological properties—would not agree with the article's conclusion. The article cites three tests in support of its preliminary conclusion that ropinirole is not centrally active. Two of them—the hexobarbital-induced sleep time test and the adenlyate cyclase test—are not tests for central D<sub>2</sub> agonist activity. Simply put, one skilled in the art would not rely on either of these tests as an indication of D<sub>2</sub> activity in the CNS.

110. The third test described in the article, the confinement motor activity test, is properly used to show central effects. Here, however, the GSK authors demonstrably misunderstood the results of their tests. The tests were said to show decreased motor confinement activity at "high" doses. (Gallagher Article at 1535.) Contrary to the article's conclusion, however, this depression of locomotor activity was *consistent* with pre-synaptic D<sub>2</sub> agonist activity in the brain (*i.e.*, in the CNS). (Bhatanagar, *Structure Activity Relationships of Presynaptic Dopamine Receptor Agonists*, Pharmacol. Biochem. & Behavior, 17(1):11-19 (1982) at 12.) Other dopaminergic agonists effective at CNS D<sub>2</sub> receptors, like apomorphine, were known to exhibit a biphasic effect on locomotor activity (*i.e.*, decreasing locomotor activity at lower doses and increasing locomotor activity at higher doses). Given that the dosage of 1 mg/kg of ropinirole described in the Gallagher article (Gallagher Article at 1535) is actually low

in comparison to the 10 mg/kg dosages of ropinirole disclosed in the '808 patent to cause antihypertensive effect, the depression on motor activity noted in the Gallagher article would actually be consistent with biphasic effects on motor activity associated with other known dopaminergic agents. Thus, one skilled in the art would have understood the results of the confinement motor activity tests to be consistent with, if not show, ropinirole's central activity.<sup>3</sup>

**D. Claim 3 Of The '860 Patent Is Anticipated By The '808 Patent**

111. Absent the erroneous statement in the '860 patent about the lack of expectation of central effects, the lack of novelty of the '860 patent is straightforward. Claim 3 merely claims the use of the '808 patent compound, ropinirole hydrochloride, for use in treating patients with Parkinson's disease. ('860 patent, col. 8, ll. 10-14.)

112. Prior to May 21, 1987, the priority date of the '860 patent, it was known that ropinirole was a pre-synaptic D<sub>2</sub> agonist in the periphery ('808 patent, col. 4, ll. 31-34); ropinirole showed strong potency in the perfused rabbit ear artery test ('808 patent, col. 4, ll. 45-48), a test that was "useful for the development of new . . . dopaminergic agonists for the treatment of parkinsonism, a disease associated with depletion of striatal dopamine" (Steinsland, O. and Hieble, J.P., *Dopaminergic Inhibition of Adrenergic Neurotransmission as a Model for Studies on Dopamine Receptor Mechanisms*, Science 199:443-45 (1978)); and other

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<sup>3</sup> Further, the methodology of the confinement motor activity (CMA) test described in the Gallagher Article is scientifically questionable. [REDACTED]

dopaminergic agonist drugs, including bromocriptine and other ergot alkaloids acted as both pre-synaptic D<sub>2</sub> agonists peripherally and post-synaptic D<sub>2</sub> agonists in the CNS ('860 patent, col. 1, ll. 36-38; Demarinis et al., *Syntheses and In-Vitro Evaluation of 4-(2-Aminoethyl)-2(3H)-indolones and Related Compounds As Peripheral Prejunctional Dopamine Receptor Agonists*, J. Med. Chem. 29:939-47 (1986)). This information would have led one skilled in the art of the '860 patent to expect that a pre-synaptic D<sub>2</sub> agonist, like ropinirole, could be used to treat Parkinson's disease, so long as sufficient quantities of the drug cross the blood-brain barrier.

113. Ropinirole does not have the catechol structure of dopamine that prevents dopamine from crossing the blood-brain barrier. One skilled in the art of the '860 patent would have expected ropinirole to cross the blood-brain barrier in therapeutically effective quantities given that its indolone structure is inherently lipophilic, which would be expected to facilitate passive diffusion across the blood-brain barrier, and its non-catechol structure makes it more resistant to enzymatic degradation in the periphery before it penetrates the blood-brain barrier.

114. As a result, one skilled in the art of the '860 patent would have had a reasonable expectation that ropinirole would be an effective anti-Parkinson's agent knowing: (1) the positive results of the perfused rabbit ear test; (2) the similarity of ropinirole to other drugs, such as bromocriptine and other ergot alkaloids, that are both pre-synaptic D<sub>2</sub> agonists peripherally and post-synaptic D<sub>2</sub> agonists in the CNS; and (3) the expected ability of ropinirole to cross the blood-brain barrier. Accordingly, claim 3 of the '860 patent is invalid as anticipated by the '808 patent.

#### **E. In The Alternative, Claim 3 Of The '860 Patent Is Obvious**

115. To the extent claim 3 of the '860 patent is not anticipated by the '808 patent, claim 3 is obvious in view of the prior art. The prior art cited above with respect to the '808 patent—including the Cannon 1981 Article and the Cannon 1978 Article—as well as subsequent

prior art including the Cannon 1986 Article—show that dopamine agonists that are structurally similar to ropinirole had been tested and confirmed to have anti-Parkinson's activity.

116. One of ordinary skill in the art of the '860 patent—knowing ropinirole was a D<sub>2</sub> agonist, knowing it would likely cross the blood-brain barrier, and knowing that similar compounds were proven anti-Parkinson's drugs—would have expected ropinirole to be useful treating Parkinson's disease, thus rendering the subject matter of claim 3 obvious.

### **1. Scope and Content Of Prior Art**

#### **a. '808 Patent**

117. As discussed above, the '808 patent discloses that ropinirole is a selective pre-synaptic D<sub>2</sub> agonist in the periphery ('808 patent, col. 4, ll. 31-34). Ropinirole shows strong potency in the perfused rabbit ear artery test ('808 patent, col. 4, ll. 45-48), which, as described above, is a test for anti-Parkinsonian activity. And, other dopaminergic agonist drugs, including bromocriptine and other ergot alkaloids, act as post-synaptic D<sub>2</sub> agonists in the CNS ('860 patent, col. 1, ll. 36-38).

#### **b. Cannon 1981 Article**

118. The Cannon 1981 Article discloses an indole (compound 9) that is very similar in structure to ropinirole, and differs from the structure of ropinirole only in that the double-bonded carbonyl oxygen of ropinirole is replaced with a double-carbon bond. The Cannon 1981 article describes this compound as the dopaminergic pharmacophore of ergot alkaloids, such as lergotrile and pergolide, which were known to treat Parkinson's disease, and notes that that the compound “induced decreased locomotion in rats,” which “indicates that it apparently crosses the blood-brain barrier.” This indole compound is described in the Cannon 1981 Article as retaining potent dopaminergic activity, which a person of ordinary skill in the art would understand to mean that this indole compound would also be useful in treating Parkinson's

disease. (Cannon 1981 Article at 240.) The Cannon 1981 Article additionally implies that the 2-position of the indole—the site that differs from ropinirole—could be modified without eliminating the efficacy of the compound in treating Parkinson’s disease, as lergotriole retains efficacy in treating Parkinson’s disease even though it includes a chlorine atom attached at the 2-position.

**c. Cannon 1986 Article**

119. Cannon, et al., *The Design of Potential Anti-Parkinsonian Drugs: What is the Dopaminergic Pharmacophore in Ergot Alkaloids?*, Proc. Iowa Acad. Sci. 93(4):69-74 (1986) (“the Cannon 1986 Article”) identifies compound 33 as the same indole compound identified as compound 9 in the Cannon 1981 Article that differs structurally from ropinirole in only one respect—the double-bonded carbonyl oxygen of ropinirole is replaced with a double-carbon bond. Like the Cannon 1981 article, the Cannon 1986 Article describes this compound as the dopaminergic pharmacophore of ergot alkaloids, such as lergotriole and pergolide, which were known to treat Parkinson’s disease. (Cannon 1986 Article at 169, 172.) Similarly, this indole compound is described in the Cannon 1986 Article as “an extremely potent/active dopaminergic agonist” and “a more specific agent with decidedly fewer side effects,” which a person of ordinary skill in the art would understand to mean that this indole compound would also be useful in treating Parkinson’s disease. (Cannon 1986 Article at 173.) The Cannon 1986 Article additionally indicates that the key features of the indole for dopaminergic activity are the benzene ring, di-n-propyl amine group on the side chain at the 4-position, and the NH group at the 1-position on the pyrrole ring. Therefore, a person of ordinary skill in the art would have understood that the 2-position of the indole—the site that differs from ropinirole—could be modified without eliminating the efficacy of the compound in treating Parkinson’s disease.

**d. Cannon 1978 Article**

120. Cannon et al., *Preparation and Biological Actions of Some Symmetrically N, N-Disubstituted Dopamines*, J. Med. Chem. 21(3):248-53 (1978) ("the Cannon 1978 Article") disclosed the dopaminergic agonist activity of diethyl dopamine and di-n-propyl dopamine at both pre-synaptic D<sub>2</sub> receptors in the periphery (as shown by the inhibition of stimulated cardioaccelerator nerve activity) and post-synaptic D<sub>2</sub> receptors in the CNS (as shown by contralateral turning in lesioned rats treated with 6-hydroxy dopamine, identified as a test for central post-synaptic D<sub>2</sub> agonist activity in, e.g., Costall, B. and Naylor, R.J., *Actions of Dopaminergic Agonists on Motor Function*, Advances in Neurology, Vol. 9 (1975)). The compound was explicitly characterized as "hav[ing] an ability to pass the blood-brain barrier and stimulate cerebral dopamine mechanisms." (Cannon 1986 Article at 251.)

**2. Claim 3 Of The '860 Patent Is Obvious**

**a. Claim 3 Is Obvious In View Of The '808 Patent Combined With The Cannon 1981 Article And/Or The Cannon 1986 Article**

121. To the extent claim 3 of the '860 patent is not anticipated by the prior art '808 patent, it is rendered obvious by the '808 patent in view of the teachings of the Cannon 1981 Article and/or the Cannon 1986 Article.

122. The structural similarity of ropinirole to the indole compound described in the Cannon 1981 and Cannon 1986 articles would have motivated a person of ordinary skill in the art of the '860 patent to combine the teachings of the '808 patent with the teachings of the Cannon 1981 article and/or the Cannon 1986 Article, and based on the combination of the information contained in these references would have expected ropinirole, a known peripheral D<sub>2</sub> agonist, to be useful in treating Parkinson's disease.

**b. Claim 3 Is Obvious In View Of The '808 Patent Combined With The Cannon 1978 Article**

123. To the extent claim 3 of the '860 patent is not anticipated by the prior art '808 patent, it is rendered obvious by the '808 patent in view of the teachings of the Cannon 1978 Article.

124. Based on the knowledge from the Cannon 1978 Article that compounds 2 and 3 of the Cannon 1978 Article are pre-synaptic D<sub>2</sub> agonists in the periphery and post-synaptic D<sub>2</sub> agonists in the CNS, as well as the knowledge from the '808 patent that ropinirole was a pre-synaptic D<sub>2</sub> agonist in the periphery, a person of ordinary skill in the art of the '860 patent would have expected that ropinirole would also be a post-synaptic D<sub>2</sub> agonist. Therefore, it would have been obvious for one of ordinary skill in the art of the '860 patent to try to use ropinirole to treat Parkinson's disease.

**F. Secondary Considerations Of Non-Obviousness Do Not Show Claim 3 Of The '860 Patent Is Non-Obvious**

125. Teva has established at least a *prima facie* case that claim 3 of the '860 patent is invalid for obviousness. No secondary considerations of non-obviousness change the conclusion that claim 3 of the '860 patent is obvious in view of the prior art. As discussed above with respect to the '808 patent, copying is not probative of non-obviousness in an ANDA case. *Eli Lilly*, 2004 WL 1724632, at n.21 ("[B]ecause the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects . . . demonstration of equivalency of [a generic version of a drug] to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention.").

126. GSK cannot point to any commercial success due to the '860 patent. As an initial matter, because the '808 patent precluded anyone else in the field from developing ropinirole,

commercial success is substantially irrelevant. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005), *cert denied*, 126 S. Ct. 488 (2005).

127. In any case, any alleged commercial success enjoyed by Requip does not demonstrate non-obviousness of the '860 patent on the facts of this case. As discussed above, Requip has not been highly commercially successful in the marketplace for drugs for the treatment of Parkinson's disease with respect to its competition. In addition, much of any commercial success that Requip has enjoyed arises from the following external factors, rather than from the claimed features of the patent invention. These external factors include: (1) use of the drug for indications other than Parkinson's disease; (2) massive efforts and funds spent on marketing, advertising, promoting, and selling the product; and (3) GSK's 8 Week Requip starter kit, which provides 8 weeks of free samples and detailed directions to counteract Requip's long and laborious titration schedule, an inherent disadvantage of the claimed invention for the treatment of Parkinson's disease.

128. GSK's arguments of unexpected results are wrong for the reasons described above with respect to the Gallagher Article. Misinterpreting data and running the wrong tests to arrive at a factually inaccurate conclusion cannot be the basis for making otherwise obvious subject matter non-obvious.

## IX.



129. Section 102(f) provides that a person shall be entitled to a patent unless "he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f). The word "he" in subsection 102(f) "refers to the specific inventive entity named on the patent." *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1349 (Fed. Cir. 1998). Thus, subsection 102(f) "mandates that a patent accurately list the correct inventors of a claimed invention." *Id.* "Accordingly, if nonjoinder of

an actual inventor is proved by clear and convincing evidence, a patent is rendered invalid.” *Id.* (internal citations omitted) (“[S]ection 102(f) still makes the naming of the correct inventor or inventors a condition of patentability; failure to name them renders a patent invalid.”).

130. “Determining ‘inventorship’ is nothing more than determining who conceived the subject matter at issue.” *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994). “Conception exists when a definite and permanent idea of an operative invention, including every feature of the subject matter sought to be patented, is known.” *Id.* “Conception is complete when one of ordinary skill in the art could construct the apparatus without unduly extensive research or experimentation.” *Id.*

A. [REDACTED]

131. [REDACTED]

[REDACTED] Claim 3 of the ‘860 patent recites “[a] method of treatment of Parkinson’s Disease which comprises administering an effective non-toxic amount for the treatment of Parkinson’s disease of [ropinirole] to a subject in need thereof.” (‘860 patent, claim 3.) [REDACTED]

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C.

If claim 3 of the '860 patent is not invalid as anticipated or obvious in view of the '808 patent, the claim is invalid under 35 U.S.C. § 102(f) for two reasons.

136.

## X. LEGAL STANDARDS FOR INEQUITABLE CONDUCT

### A. Inequitable Conduct

137. “The inequitable conduct analysis is performed in two steps comprising ‘first, a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent in light of all the circumstances to determine whether the applicant’s conduct is so culpable that the patent should be held unenforceable.’” *Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1186 (Fed. Cir.), *cert. denied*, --S. Ct.--, 75 USLW 3121 (U.S. Oct. 30, 2006) (No. 06-372) (quoting *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1362-63 (Fed. Cir. 2003) and *Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1366 (Fed. Cir. 2001)).

138. “While inequitable conduct includes affirmative misrepresentations of material facts, it also arises when the patentee fails to disclose material information to the PTO.” *Ferring*, 437 F.3d at 1187.

139. “The predicate facts must be proven by clear and convincing evidence.” *Id.*

140. Materiality and intent to deceive are distinct factual inquiries. “The more material the conduct, the less evidence of intent will be required in order to find that inequitable conduct has occurred.” *Perceptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1319 (Fed. Cir. 2000).

141. Inequitable conduct as to any aspect of a patent’s prosecution renders the entire patent and each of its claims unenforceable. *Praxair, Inc. v. ATMI, Inc.*, 445 F. Supp. 2d 473, 478 (D. Del. 2006) (“If it is established that a patent applicant engaged in inequitable conduct with respect to one claim, then the entire patent application is rendered unenforceable”).

Accordingly, a patent claim may be rendered unenforceable, even though the inequitable conduct at issue is not directly related to that claim. *See id.*

#### **B. Materiality**

142. “For patent applications that have been prosecuted prior to 1992, we have held that ‘[i]nformation is deemed material if there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent.’” *Ferring*, 437 F.3d at 1187 (quoting 37 C.F.R. § 1.56 (1989)).

143. A patent applicant’s omission or misrepresentation can be material to patentability even if a reasonable patent examiner would not have rejected the patent application but for the alleged inequitable conduct. *Hoffman-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1367-68 (Fed. Cir. 2003).

144. Because proceedings before the PTO are conducted *ex parte*, it is especially important that the patent examiner has all of the information necessary to determine whether and to what extent he should rely on declarations presented by the applicant. *See Ferring*, 437 F.3d at 1187.

145. As a matter of law, declarations and affidavits submitted to the PTO in support of a pending patent application “are inherently material.” *Refac Int’l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1583 (Fed. Cir. 1996). Indeed, “[t]he affirmative act of submitting an affidavit must be construed as being intended to be relied upon.” *Id.*

146. Misrepresentations in a patent regarding the actual performance of experiments and results of those experiments can be material when relied upon to establish the patentability of a claimed invention. *Hoffman-La Roche*, 323 F.3d at 1366-7.

### C. Intent to deceive

147. Patent applicants “are required to prosecute patent applications in the [Patent and Trademark Office (PTO)] with candor, good faith, and honesty.” *See Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995). The duties of candor, good faith and honesty extends to an applicant’s representatives, whose “knowledge and actions . . . are chargeable to the applicant.” *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 n.8 (Fed. Cir. 1987). The duty “rests on the inventor, on each attorney or agent who prepares or prosecutes the application, and on every other individual who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor” or the assignee. *Molins*, 48 F.3d at 1178 n.6.

148. A breach of an applicant’s duties of candor, good faith, and honesty when prosecuting a patent application can lead to a finding that the applicant engaged in inequitable conduct before the PTO. *See Life Techs., Inc. v. Clonitech Labs., Inc.*, 224 F.3d 1320, 1324 (Fed. Cir. 2000). The effect of a finding of inequitable conduct is to render the patent unenforceable. *See id.*

149. Intent is a separate element of inequitable conduct. Even if an omission or misrepresentation is found to be material, intent may not be presumed. *Ferring*, 437 F.3d at 1190. Intent need not, however, be proven by direct evidence, and in fact rarely can be so proven. *See Hoffman-La Roche*, 323 F.3d at 1371 (“Intent, however, is typically proved inferentially, ... and a finding of intent does not require a confession from the stand by the inventor or the prosecuting attorney,” citing *Molins, Inc.*, 48 F.3d at 1180; *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed. Cir. 1989). Intent can be proven through circumstantial evidence, and “in the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose

material information.” *Bruno Independ. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005). “[A] patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish ‘subjective good faith’ sufficient to prevent the drawing of an inference of intent to mislead.” *Ferring*, 437 F.3d at 1191 (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997)).

150. Where a party-patentee has invoked the attorney-client communication or attorney work product privilege to prevent discovery regarding the applicant’s intent to deceive the Patent Office, the patentee cannot then present evidence, e.g., inventor testimony or affidavits, of “subjective good faith.” *Tracinda Corp. v. DaimlerChrysler AG*, 362 F. Supp. 2d 487, 513 (D. Del. 2005); *see also Synalloy Corp. v. Gray*, 142 F.R.D. 266, 269 (D. Del. 1992).

#### **D. Patentability Issues Related To Teva’s Inequitable Conduct Defenses**

151. Teva’s inequitable conduct defenses involve issues related to patentability, including inventorship and utility.

##### **1. Inventorship**

152. “Conception is the touchstone of inventorship.” *Bayer Ag v. Housey Pharms., Inc.*, 2002 WL 31433303, at \*1 (D. Del. June 20, 2002) (quoting *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1227 (Fed. Cir. 1994)). The inventor(s) of a patent claim is/are the individual(s) responsible for conception of the invention. *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998) (“The ‘inventor,’ in patent law, is the person or persons who conceived the patented invention”). By the same token, a patent’s claim should be limited in scope to “the subject matter which the applicant regards as his invention.” 35 U.S.C. § 112 ¶2. If an individual is responsible for the conception of all or part of any claim of the patent, that individual must be named as an inventor for the entire patent. *Ortho-McNeil Pharm., Inc. v.*

*Mylan Labs, Inc.*, 2006 WL 1517749, at \*9 (D.N.J. May 30, 2006) (citing *Burroughs Wellcome Co.*, 40 F.3d at 1227-28). “When an invention is made by two or more persons jointly, they shall apply for patent jointly and each make the required oath.” 35 U.S.C. § 116. Accordingly, the patent applicant must disclose all of the inventors of a patent during prosecution. *Id.*

153. Because an examiner must attend to the question of inventorship, pursuant to 35 U.S.C. § 102(f), omissions or misrepresentations regarding the inventorship of a patent is material. *Perceptive Biosystems*, 225 F.3d at 1321-22 (“As a critical requirement for obtaining a patent, inventorship is material.”).

154. “[W]hether the inventorship of the patents as issued is correct does not determine the materiality of the statements” regarding inventorship, “just as whether concealed prior art would actually invalidate the patent is irrelevant to materiality.” *Id.* Thus, a patent applicant’s attempt to cure an error in naming inventors is irrelevant to determining whether statement or omissions regarding inventorship constitute inequitable conduct. *Id.*

155. “Conception is the ‘formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.’” *Amgen*, 927 F.2d at 1207. “Conception requires both the idea of the invention’s structure and possession of an operative method of making it.” *Id.*

156. “[C]onception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it.” *Id.* “Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.” *Id.*

## 2. Utility/Enablement

157. To be patentable, a claimed invention must have utility, *i.e.*, information related to the utility requirement is material. *Wesley Jessen Corp. v. Bausch & Lomb, Inc.*, 209 F. Supp. 2d 348, 396-97 (D. Del. 2002), aff'd, 56 Fed. Appx. 5003 (Fed. Cir. Feb 12, 2003) (*citing Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999)). Moreover, to satisfy the enablement requirement of 35 U.S.C. § 112 ¶1 for a genus claim, the patentee must “provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims.” *Amgen*, 927 F.2d at 1213.

158. “An applicant is not entitled to a claim for a large group of compounds merely on the basis of a showing that a selected few are useful and a general suggestion of a similar utility in the others.” *In re Cavallito*, 282 F.2d 357, 361 (C.C.P.A. 1960). Where a patent claims a number of chemical compounds that “have certain basic structures in common, but may differ widely as to the addition or variation of substituents at specified points,” the patent applicant must present evidence that the utility ascribed to the entire group of compounds is derived solely from the basic structural formula common to all of them and “that changes in substituents did not affect the basic utility of the compounds.” *Id.* at 362. Absent such evidence, utility for the broad genus of claimed compounds is not shown by evidence that a selected few of the claimed compounds has such utility. *Id.*

159. Where the patent examiner does not request specific evidence of the utility of all of the compounds within a claimed genus, it is reasonable to assume that he accepted statements in the patent itself stating that the claimed compounds have the desired utility as establishing that all of the claimed compounds have the required common utility. *See, e.g., id.* (Patent examiner presumed to have relied upon statement in patent that “The compounds have utility as hypotensive agents.”)

## XI. THE '808 PATENT IS UNENFORCEABLE FOR INEQUITABLE CONDUCT

A.

160. The '808 patent names Mr. Gallagher as the its sole inventor. (DTX 42.)

167.

168. Claims 8-12 of the '808 patent cover “[a] pharmaceutical composition having D<sub>2</sub> receptor agonist activity comprising a nontoxic, agonist quantity” of one of the claimed compounds. Thus, in order to conceive of these claimed inventions, the inventor(s) must have been the first to appreciate that the compounds in question acted as D<sub>2</sub> receptor agonists.

170.

171. Claim 1 covers a broad genus of chemical compounds that includes more than a thousand particular species, only one of which is ropinirole. Claim 8 covers pharmaceutical compositions including this same genus of compounds. Thus, in order to conceive of the claimed invention, the inventor(s) must have had a definite and permanent idea of the structure of each of the claimed compounds and how they would be used. While this does not necessarily mean that all of the compounds had to be tested, the inventor(s) must have believed that the compounds were useful to cause the cardiovascular effects described in the '808 patent.

176.

177. Misrepresentations regarding the inventorship of a claimed invention are inherently material. *Perceptive Biosystems*, 225 F.3d at 1321-22 (“As a critical requirement for obtaining a patent, inventorship is material.”).

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B. [REDACTED]

[REDACTED]

[REDACTED]

187. As noted above, Mr. Gallagher and GSK's patent attorneys owed a duty of candor to the Patent Office. [REDACTED]

[REDACTED]

[REDACTED]

188. To distinguish the compounds claimed by the '808 patent from the prior art '944 patent compounds, the '808 patent states that the ropinirole does not exhibit tachyphylaxis and that the remaining compounds claimed in the '808 patent may not exhibit tachyphylaxis. Specifically, the '808 patent specification states that the claimed compounds "may not be subject to tachyphylaxis . . . when compared with the prior art compounds based on preliminary pharmacological tests with the preferred species of this invention" ('808 patent, col. 1, ll. 48-53) and the compound of the preferred embodiment, ropinirole hydrochloride, "did not cause tachyphylaxis . . . as did its 7-hydroxy congener [*i.e.*, the corresponding compound disclosed in GSK's '944 patent and identified in the '808 patent as "SK&F 89124"] of the prior art" in one of the *in vivo* tests (hind limb) performed in dogs (*Id.* at col. 4, ll. 48-52).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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C. [REDACTED]

198. As noted above, the '808 patent states that "the compounds of this invention, especially 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride, have proved to be selective peripheral D<sub>2</sub> -agonists" (DTX 42, col. 4, ll. 31-34.) Notably, the only compound for which actual experimental results are disclosed in the '808 patent specification is ropinirole. (*Id.*)

[REDACTED] Mr. Gallagher was GSK's representative with respect to the conception and reduction to practice of the inventions claimed in the '808 patent. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

200. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A series of 15 thick black horizontal bars of varying lengths, arranged vertically from top to bottom. The bars are evenly spaced and extend across the width of the page.

201. The '808 patent further states that "[f]or an average size human using 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride [*i.e.*, ropinirole hydrochloride] as an active ingredient, a typical dose to show anti-hypertensive activity would be selected from the range of from about 100-250 mg of base equivalent for each dosage unit which is adapted for oral administration and which is administered orally from 1-4 times daily." (DTX 42, col. 5, l. 67-col. 6, l. 5.) For the other claimed compounds, the '808 patent states:

Preferably, the compositions will contain the active ingredient in an active but nontoxic quantity selected from the range of about 50 mg to about 500 mg, preferably about 75-250 mg, of active ingredient, as the base, per dosage unit. This quantity depends on the relative potency of the base compound compared with that of the prototypal species, 4-(2-di-n-propylamino-ethyl)-2(3H)-indolone,

as well as on the specific biological activity desired, the route of administration, that is, whether oral or parenteral, and the condition and size of the patient.

(*Id.*, col. 5, ll. 6-16.)

Advantageously, doses selected from the dosage unit ranges given above will be administered several times, such as from one to five times, a day. The daily dosage regimen is selected from the range of about 50 mg to about 1.0 g, preferably 200-750 mg for oral administration and 50-500 mg for parenteral administration. When the method described above is carried out, D.sub.2 -agonist activity is produced.

(*Id.*, col. 5, ll. 59-66.)



207

## XII. THE '860 PATENT IS UNENFORCEABLE FOR INEQUITABLE CONDUCT

A.

208. Claim 1 of the '860 patent covers the use of any one of a genus of compounds to treat Parkinson's disease. The genus includes more than a hundred particular species of compounds, one of which is ropinirole disclosed in the prior art '808 patent and another of which is SK&F 89124 disclosed in the prior art '944 patent. The true inventor(s) of claim 1 of the '860 patent had to have conceived of the entire scope of this claimed invention by forming a definite and permanent idea that some amount of each of the claimed compounds would be effective to treat Parkinson's disease in patients.

The image shows a single page with 21 horizontal black redaction bars. The bars are of varying lengths, with some being relatively short and others being very long, covering most of the page. The redaction bars are positioned in a staggered pattern, with some appearing in pairs and others appearing alone. The background of the page is white.

For example, compound 31 of the DeMarinis Article is the claimed compound in which R is an n-propyl ( $C_3\text{Alkyl}$ ) group,  $R^1$  and  $R^2$  are both methyl ( $C_1\text{alkyl}$ ) groups,  $R^3$  is hydroxy group, and n is 2. The DeMarinis Article describes compound 31 as dopaminergically inactive.

A series of horizontal black bars of varying lengths, likely representing redacted text or a visual effect. The bars are positioned in a grid-like pattern across the page. The lengths of the bars decrease from top to bottom, creating a descending staircase effect. The bars are solid black and have a thin white border.

218. The '860 patent describes existing treatments for Parkinson's disease as including various ergot derivative compounds. Specifically, the '860 patent states:

An alternative form of therapy is to administer *postsynaptic* dopamine agonists, for example ergot alkaloids such as bromocriptine – however, this approach is also associated with side-effects.

(‘860 patent, col. 1, ll. 36-39 (emphasis added).) The patent goes on to describe the “particularly interesting” finding that ropinirole was also a post-synaptic D<sub>2</sub> agonist:

It has now been found that certain indolone derivatives known in the art as pre-synaptic D<sub>2</sub>-agonists having utility as cardiovascular agents (see EP No. 113964-B), also are post-synaptic D<sub>2</sub>-agonists in the brain and hence are expected to have utility in the treatment of Parkinsonism.

(*Id.*, col. 1, ll. 48-53.) This statement creates a misleading distinction between pre- and post-synaptic D<sub>2</sub> receptors, which are identical for all intents and purposes relevant to this case. ■

The image shows a page with a grid-like pattern of horizontal black bars used for redaction. A large, solid black rectangular box is placed in the upper-middle portion of the page, partially overlapping some of the redaction bars. Within this large black box, the words 'CONFIDENTIAL' and '100-00000' are faintly visible in white, suggesting they were part of the original document before being redacted. The rest of the page is white with no other content.

223.

**XIII. CONCLUSION**

224. In light of the foregoing findings of fact and conclusions of law, the Court finds as follows:

- (1) Claim 5 of the '808 patent is invalid for obviousness under 35 U.S.C. § 103;
- (2) Claim 3 of the '860 patent is invalid as anticipated under 35 U.S.C. § 102;
- (3) Claim 3 of the '860 patent is invalid for obviousness under 35 USC § 103;
- (4) In the alternative, if claim 3 is not invalid in view of the prior art, claim 3 is invalid under 35 U.S.C. § 102(f);
- (5) The '808 patent is unenforceable for inequitable conduct; and
- (6) Is the '860 patent is unenforceable for inequitable conduct.

## EXHIBIT 22 TO PROPOSED PRETRIAL ORDER

**GSK'S LIST OF WITNESSES****I. Witnesses GSK Will Call in Person or By Deposition**

At this time, before receipt of Teva's final witness list or any other pretrial order exhibits, Plaintiff GlaxoSmithKline ("GSK") expects to call at least the following witnesses during its case in chief either in person or by deposition. GSK also expressly reserves the right to call any individual listed on Teva's witness list.

**I. Witnesses GSK Will Call in Person or By Deposition**

- (a) Dr. Paul A. Bartlett  
Department of Chemistry  
University of California  
Berkeley, CA 94720
- (b) Mr. Egon E. Berg  
502 Airport Exec. Park  
Nanuet, NY 10954
- (c) Mr. Gregory Gallagher, Jr.  
7632 Harrington Lane  
Bradenton, FL 34202
- (d) Dr. Peter G. Jenner  
Neurodegenerative Diseases Research Centre  
GKT School of Biomedical Sciences  
Hodgkin Building  
King's College London  
London SE1 1UL  
United Kingdom
- (e) Dr. David A.A. Owen  
Coppice Farm, Stanton Upon Hine Heath  
Shrewsbury, Shropshire SY4 4ET  
United Kingdom
- (f) Dr. Lewis Sudarsky  
Brigham & Women's Hospital  
Department of Neurology  
75 Francis Street  
Boston, MA 02115

## EXHIBIT 22 TO PROPOSED PRETRIAL ORDER

(g) Dr. Christopher A. Velturo  
Quantitative Economic Solutions, LLC  
1280 Massachusetts Avenue  
Cambridge, MA 02138

**II. Witnesses GSK May Call In Person or By Deposition**

In addition, at this time, before GSK has received Teva's portions of the pretrial order, GSK may call one or more of the following witnesses in person or by deposition.

- (a) Professor Brenda Costall  
University of Bradford  
Richmond Road, Bradford  
West Yorkshire BD7 1DP  
United Kingdom
- (b) Mr. Roger Eden  
242 Daniells, Welwyn  
Garden City, Herts AL7 1QQ  
United Kingdom
- (c) Mr. Richard D. Foggio  
P.O. Box 83  
Bedminster, PA 18910
- (d) Dr. Peter J. Giddings  
GlaxoSmithKline Services Unlimited  
980 Great West Road  
Brentford, Middlesex TW8 9GS  
United Kingdom
- (e) Dr. Carol A. Harvey  
GlaxoSmithKline  
2301 Renaissance Blvd.  
King of Prussia, PA 19406
- (f) Dr. Paul Hieble  
GlaxoSmithKline  
709 Swedeland Road  
King of Prussia, PA 19406
- (g) Dr. William Huffman  
GlaxoSmithKline  
709 Swedeland Road  
King of Prussia, PA 19406

## EXHIBIT 22 TO PROPOSED PRETRIAL ORDER

- (h) Ms. Deborah Jaskot  
Teva Pharmaceuticals USA, Inc.  
North Whales, PA
- (i) Ms. Anne Payne  
Teva Pharmaceuticals USA, Inc.  
North Whales, PA
- (j) Mr. Kevin Reeves  
GlaxoSmithKline  
5 Moore Drive  
Research Triangle Park, NC 27789
- (k) Mr. Stuart R. Suter  
505 Leamington Court  
Amber, PA 19002
- (l) GSK Document Custodian
- (m) Any individual listed on Teva's witness list

GSK provides this initial witness list pursuant to the parties' agreement to jointly prepare a pre-trial order in compliance with the Court's standing order for final pre-trial orders. GSK's initial list provided to defendants is without prejudice to GSK's right to object to any individual on defendant's witness list, including individuals on GSK's witness list. GSK reserves the right to amend this list as circumstances warrant, including to the extent the Court precludes or permits particular witness testimony.

## EXHIBIT 23 TO PROPOSED PRETRIAL ORDER

### TEVA'S MISCELLANEOUS ISSUES TO BE ADDRESSED AT PRETRIAL CONFERENCE

1. Whether GSK should be permitted to call witnesses not timely disclosed, as referenced in Exhibit 11, Teva's Objections to GSK's witness list.
2. How the Court wishes to receive testimony by deposition, and how the Court intends to allocate time, if any, as to those depositions.
3. Teva proposes that, by 6:30 p.m., two days before using an exhibit at trial the party using the exhibit shall identify to opposing counsel in writing all exhibits (including demonstrative exhibits) that it will use on direct examination for witnesses called on that day. Except for exhibits created during testimony or used during cross-examination, no exhibits will be used at trial unless so identified.
4. Teva proposes that the parties agree that notice of a party's intended use of blowups (enlargements) of admitted trial exhibits need not be given (and need not be exchanged as a demonstrative exhibit), whether or not highlighted, as long as the party had identified its intention to use the trial exhibit according to the preceding paragraph.
5. Teva proposes that, by 6:30 p.m., two days before calling a witness in person at trial, the calling party shall notify opposing counsel in writing of its intention to call that witness on that day, along with an identification of the trial exhibits that it expects to use on direct examination of that witness, including demonstrative exhibits. The calling party shall not call a witness at trial unless so identified or unless the other party failed to inform the calling party that it intended to finish its case the next day.

The parties are still conferring about other issues, and if they do not reach agreement, Teva may have additional issues that it wishes to raise with the Court.

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

SMITH KLINE & FRENCH	)	
LABORATORIES LIMITED and	)	
SMITHKLINE BEECHAM	)	
CORPORATION d/b/a	)	
GLAXOSMITHKLINE,	)	
	)	
Plaintiffs,	)	Civil Action No. 05-197-GMS
v.	)	
	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
	)	
Defendant.	)	
	)	

PLAINTIFFS' STATEMENT OF INTENDED PROOF

Plaintiffs Smith Kline & French Laboratories Limited, and SmithKline Beecham Corporation d/b/a GlaxoSmithKline (collectively "GSK") set forth below a brief statement of what it intends to prove at trial and reserves the right to supplement this exhibit and/or the proofs offered at trial.

**L. The Nature of the Case**

This is a patent infringement action in which GSK contends that Teva infringes claim 5 of U.S. Patent No. 4,452,808 ("the '808 patent") and claim 3 of U.S. Patent No. 4,824,860 ("the '860 patent"). GSK developed, makes and sells REQUIP®, which is used to treat patients suffering from Parkinsons Disease and Restless Legs Syndrome ("RLS"). SmithKlineBeecham Corporation d/b/a GSK is the owner of the '808 patent.

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

Claim 5 of the '808 patent is a claim to a chemical composition that covers ropinirole hydrochloride, the chemical name for REQUIP. Claim 3 of the '860 patent is a method claim directed to the use of ropinirole hydrochloride to treat Parkinsons Disease. In December 2004, Teva filed an Abbreviated New Drug Application ("ANDA") to obtain approval from the United States Food and Drug Administration ("FDA") to engage in the commercial manufacture and sale of ropinirole hydrochloride tablets, prior to the expiration of GSK's patents. Teva's ANDA submission constituted an act of infringement under 35 U.S.C. §271(e)(2) of the asserted claims.

Teva's primary defense is that claim 5 of the '808 patent and claim 3 of the '860 patent would have been obvious. Teva also asserts that these claims are unenforceable because of alleged acts of inequitable conduct committed with respect to both patents by the named inventors. GSK contends that both patents are valid and enforceable and that Teva has not met, nor can it meet, the heavy burden of proving otherwise.

## II. Background

*Dopamine* is a chemical substance that acts as a *neurotransmitter* in the *central nervous system* ("CNS") and plays an important role in controlling movement.<sup>1</sup> A *dopamine agonist* is a chemical compound that mimics the actions of dopamine in the body.

Parkinson's Disease causes the degeneration of dopamine-containing nerves running between the *substantia nigra* and the *striatum*, two parts of the brain that control motion in the body. The absence of dopamine causes nerve cells to fire uncontrollably and results in slowness, stiffness, and tremor. The symptoms of Parkinson's Disease include slowness of movement (called "*bradykinesia*"), stiffness, tremor, stooped posture, imbalance, and shuffling gait.

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<sup>1</sup> Italicized terms are defined in Attachment A to GSK's Proposed Findings of Fact and Conclusions of Law (Exhibit 20).

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

To maintain mobility, the dopamine normally released by the brain in a healthy person must be replaced with medication. Dopamine agonists are used as one method of treatment of Parkinson's Disease because they mimic the action of the dopamine which has been lost as a result of the disorder. REQUIP is a dopamine agonist and is used on its own or in combination with other drugs to treat Parkinson's disease.

Restless Legs Syndrome ("RLS") is an awake phenomenon characterized by an intense, irresistible urge to move the legs, usually associated with sensory complaints; motor restlessness; worsening of symptoms at rest and relief with motor activation; and increased severity in the evening or at night. RLS affects approximately 1 in 10 adults in the U.S. Symptoms may begin at any age, but peak onset is in middle age. The severity of RLS symptoms may fluctuate greatly throughout a patient's lifetime. REQUIP is the first drug approved by the FDA for treatment of RLS. The precise mechanism of action of REQUIP for treatment of RLS is unknown, but the dopaminergic system appears to be involved.

### III. The Patents-In-Suit

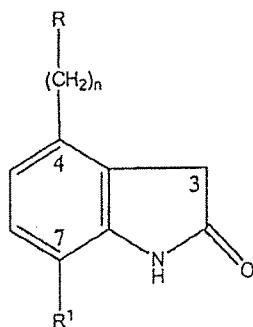
#### A. The Invention of Ropinirole

The story of the invention of ropinirole begins with the invention of an earlier compound first described in a prior GSK patent, U.S. Patent No. 4,314,944 ("the '944 patent"), naming Dr. William Huffman and Dr. James Wilson as inventors. Dr. Huffman worked as part of the chemistry group at GSK looking for compounds with beneficial cardiovascular activity. As part of this program, Dr. Huffman synthesized some compounds in the hope that they would mimic dopamine. Dr. Huffman's work led to the compound known as SKF 89124.

The hypothesis underlying Dr. Huffman's work at the time was that in order for a compound to mimic dopamine, that compound must have either a *catechol* or a *catechol mimetic*. A catechol is a benzene ring with two adjacent *hydroxyl groups* substituted and, at that time, was

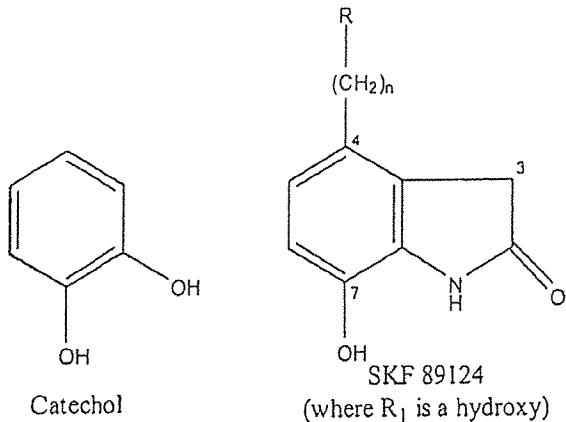
## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

thought to be responsible for a compound's dopaminergic activity. A catechol mimetic is a compound or a portion of a compound that mimics the chemical and biological responses of a catechol. SKF 89124 was the basis for the '944 patent which discloses a new group of 2(3H)-indolones whose structures are characterized by a 2(3H)-indolone (oxindole) nucleus having an aminoalkyl substituent at the 4-position and an oxygen function at the 7-position. The generic formula claimed in the '944 patent is shown below:



SKF 89124 is considered a catechol mimetic because the R<sup>1</sup> substituent (which can be a hydroxyl (-OH) or methoxy (-CH<sub>3</sub>O) group) and the nitrogen of the pyrrole ring to the right of the benzene ring mimic the hydroxyl groups that are present on a true catecholamine, as shown below.

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER



In 1982, Gregory Gallagher was a medicinal chemist working in the GSK anti-anginal/anti-hypertensive program and was assigned to work with the Huffman compound, SKF 89124.

**REDACTED**

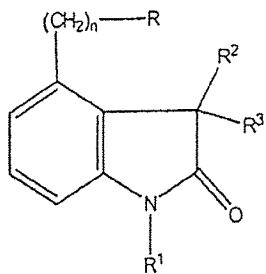
**B. The '808 Patent Disclosures And Claims**

Soon after this discovery, the GSK patent department drafted a patent application to secure protection for the invention of ropinirole. The application for the '808 patent was filed on December 7, 1982, and named Mr. Gallagher as the sole inventor. The patent discloses in its specification the closest prior art – the compounds identified in the '944 patent – and explained why Mr. Gallagher's invention was not obvious in light of that art. The '808 patent describes two different methods, labeled as Scheme A and Scheme B, by which to synthesize the 4-

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

aminoalkyl-2(3H)-indolone compounds disclosed in the '808 patent. Claim 1 of the '808 patent is recited below:

A compound of the structural formula:



in which: n is 1-3, R is amino, C<sub>1-6</sub>-lower alkylamino, di-(C<sub>1-6</sub>-lower alkyl)amino, allylamino, diallylamino, N-(C<sub>1-6</sub>-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are, each, hydrogen or C<sub>1-4</sub>-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

Claim 4 is directed to ropinirole: "The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone as the free base."

The structure of ropinirole is as follows:

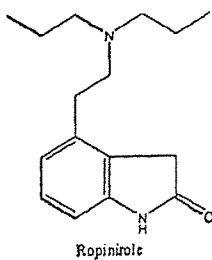


EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

Claim 5 – the '808 claim at issue in this case – claims ropinirole hydrochloride itself; that is, ropinirole that has been modified by adding a salt, hydrochloride: "The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride."

Mr. Gallagher's claims were allowed by the Patent Office in a First Office Action, and the '808 patent issued on June 5, 1984.

**C. The Invention of Ropinirole As A Treatment For Parkinson's Disease**

In the fall of 1985, further development of SKF 101468 (as ropinirole was then called) was transferred from GSK's operations in the United States to its facilities in Welwyn, England ("Welwyn")

**REDACTED**

In 1985, Dr. David Owen was the head of the Pharmacology Department at Welwyn and the senior pharmacologist responsible for cardiovascular programs in the UK

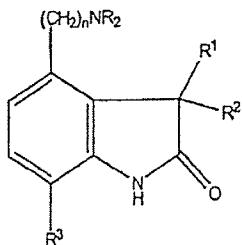
**REDACTED**

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

**REDACTED****D. The '860 Patent Disclosure And Claims**

The application for the '860 patent was filed on May 19, 1988 and named Dr. Owen as the sole inventor. A U.K. patent application, upon which the U.S. '860 application claims priority, was previously filed on May 21, 1987. The indolone derivatives disclosed in the '860 patent include some of the compounds disclosed in the '944 and '808 patents. The '860 patent discloses the discovery that these prior art indolone compounds, previously known to be peripheral dopamine agonists, exhibit central nervous system effects and could be a successful treatment for Parkinsons Disease. Claim 1 of the '860 patent is recited below:

A method of treatment of Parkinsons Disease which comprises administering an effective non-toxic amount for the treatment of Parkinsons Disease of a compound of the following structure:



in which each group R is hydrogen or C1-4 alkyl; R1 and R2 are each hydrogen or C1-4 alkyl; R3 is hydrogen or hydroxy; and n is 1 to 3; or a pharmaceutically acceptable salt thereof to a subject in need thereof.

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

Claim 3 is directed to a method of treatment of Parkinsons Disease with ropinirole: "A method of treatment of Parkinsons Disease which comprises administering an effective non-toxic amount for the treatment of Parkinsons Disease of 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride to a subject in need thereof."

**IV. The '808 and '860 Patents Are Valid**

**A. The '808 Patent Is Not Obvious**

**1. The '808 Patent Is Not Obvious In Light of the Prior Art**

Teva's sole claim of invalidity with respect to the '808 patent is that the compound of claim 5, ropinirole hydrochloride, would have been obvious to one of ordinary skill in the art at the time of the invention. In support of its obviousness contention, Teva cites various scientific publications which it claims would have made it obvious to modify a chemical compound existing in the prior art to make ropinirole hydrochloride.

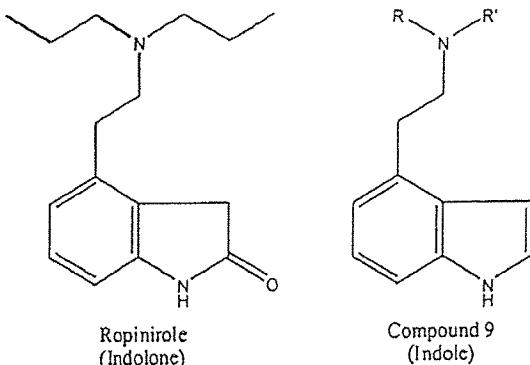
In the chemical arts, obviousness requires one of ordinary skill in the art to have a reasonable expectation of success. "[O]bvious to try" is an incorrect standard. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). Here, a person of ordinary skill in the art at the time of the invention would have been an individual with an advanced degree (M.S. or Ph.D.) in organic chemistry or pharmacology and having two or three years of laboratory experience in medicinal chemistry in an academic or industry setting. A person without a graduate degree, but having more laboratory experience in this field, could also be considered a person of ordinary skill at the time of the invention. While Gregory Gallagher did not have any advanced degree in chemistry, he had been working as a medicinal chemist at GSK for approximately 15 years at the time of his invention.

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

In challenging the '808 patent as obvious, Teva relies on an analysis called "Structure-Activity Relationships (SAR)." Teva contends that it would have been obvious to modify an existing chemical compound to make ropinirole hydrochloride and that a person of ordinary skill in the art would have expected it to be suitable as a pharmaceutical compound. Medicinal chemists apply SAR by looking for relationships and trends between the chemical structure of compounds and their biological effects. SAR analysis may be of potential use in guiding a medicinal chemist in his or her decisions about what compounds to make or avoid. However, the utility of such hypotheses is critically dependent on the type of data from which they are derived and on the nature of the extrapolation that the researcher makes in applying them to an unknown structure. In other words, the more factors that could be responsible for a compound's effect in the body, the less a scientist can rely on a change in a chemical structure to explain it.

The main thrust of Teva's obviousness challenge to the '808 patent is the existence of a substance known as "Compound 9" at the time of the synthesis of ropinirole. The structural difference between ropinirole and Compound 9 lies at the 2 position of the heterocyclic ring. In ropinirole there is a *ketone group* at the 2 position, but in compound 9 there is a carbon-carbon double bond between the 2 and 3 position. The consequence of this change is that the heterocyclic ring is no longer aromatic. This change in aromaticity can often affect how a molecule will interact with a receptor. Further, the presence of the ketone group changes the acidity of the hydrogen attached to the nitrogen. The hydrogen is now more acidic which makes it more available for hydrogen bonding with the receptor. A structural change can appear deceptively simple. In the diagram comparing ropinirole and Compound 9 below, it appears on the surface that all that Mr. Gallagher did was a simple substitution at the 2 position of the heterocyclic ring.

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER



However, the above comparison between ropinirole and compound 9 is a prime example of why two-dimensional chemical drawings provide an incomplete picture of changes in chemical structure. Receptors are three-dimensional in nature and require certain three-dimensional structure, electronic character and polarity characteristics of the compound before it can properly bond with modulate the activity of receptor. Therefore, the above drawings cannot convey any of the changes in electron distribution that results from the loss of aromaticity in ropinirole, nor do they convey the increased availability of the hydrogen for bonding with the receptor. Teva's obviousness argument regarding Compound 9 fails to take into account the three-dimensional, electronic and polar nature of compounds.

Moreover, the actual activity of Compound 9 in animals demonstrates just how difficult it is to predict whether a chemical compound will have dopaminergic activity based on its structure alone. An article summarizing research performed in 1981 by Teva's own expert, Dr. Joseph Cannon, confirms that the application of SAR analysis is unreliable in the context of dopaminergic compounds. See Cannon, J.G., Long, J.P. & Bhatnagar, R., Future directions in dopaminergic nervous system and dopaminergic agonists. *J. Med. Chem.* 24, 1113-1118 (1981) ("the 1981 Cannon Review Article"). Dr. Cannon proposed Compound 9 as the pharmacophore

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

(*i.e.*, the portion of a molecule responsible for its biological activity) to explain the dopaminergic activity of dopamine agonists known as ergot alkaloid derivatives.

Dr. Cannon hypothesized that Compound 9 demonstrates dopaminergic activity in the absence of hydroxy groups. However, Dr. Cannon also concluded that the activity of Compound 9 *in vivo* in cats required 30-40 minutes to become maximal following intravenous administration. This was significant because it meant that the dopaminergic activity observed for Compound 9 was not due to Compound 9 itself. Rather, the observed activity required that compound 9 was metabolized, after injection, to a different compound-a hydroxylated compound-in the cat's body. In other words, Compound 9 was a "prodrug," which means it was a compound that itself has little or no biological activity on its own but which becomes biologically active only after it is metabolized by the body, either by adding or subtracting functional chemical groups to or from the prodrug. Dr. Cannon ultimately confirmed that his supposedly active dehydroxylated Compound 9 was hydroxylated in the body and all the observed agonist activity was due to the hydroxylated metabolite and not Compound 9. The fact that no relationship could be drawn, even by Dr. Cannon himself, between just the chemical structure of Compound 9 and its dopaminergic activity underscores the difficulty of predicting the biological effect of a compound based singularly on its structure. Drs. Cannon and Long believed at the time, and still do today, that Compound 9 was metabolically activated by a hydroxyl group and this demonstrates that at the time a hydroxy group, which ropinirole lacks, was viewed as important for dopaminergic activity/receptor binding.

Moreover, the ring nitrogen of the indole would not be bioisosteric with a catechol hydroxy group. The indole lacks the ketone group at position 2 and the double bond is not sufficiently strong to withdraw electron density away from the nitrogen, which is what activates

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

the hydrogen for hydrogen bonding to the receptor, and in fact results in the nitrogen being a hydrogen acceptor; thus reducing its ability to bond with the receptor.

Teva's obviousness theory also suggests that the compound described in the '944 patent or compound 9 of the Cannon 1981 article would have been natural starting points for a person of ordinary skill in the art having no knowledge of ropinirole, and that such a person would be motivated to try to modify these compound over other possibilities. Yet, the 1981 Cannon Review article shows that, at the time of the invention, there were numerous structural classes of compounds with reported dopaminergic properties. An individual with ordinary skill in the art could have pursued any one of these structures to research. Dr. Cannon's own work confirms the breadth of options facing a medicinal chemist at that time.

Teva's arguments also ignore the overall state of the art in 1982. The hydroxy indolone structure from the '944 patent was not mentioned in an extensive review article that Dr. Cannon published in 1983 which covers a group of chemical structures with dopaminergic activity that is even larger than his earlier review. See Cannon, J.G. Structure-activity relationships of dopamine agonists. *Annu. Rev. Pharmacol. Toxicol.* 23, 103-129 (1983). Nor was it mentioned in the updated overview of the field published that year in *Annual Reports in Medicinal Chemistry*. De Paulis & Läkemedel, *Ann. Rep. Med. Chem.*, 18, 21-29 (1983). There was no teaching in the art at the time that would have motivated a person skilled in the art at that time to select the '944 patent compound as a starting place for further experimentation.

Finally, Teva's experts, Drs. Cannon and John Paul Long, were above ordinary skill in this art and they were particularly interested in improved dopamine agonists. They, perhaps more than anyone else, had the opportunity to consider modifications to Compound 9. Yet, the fact

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

remains that they never came up with the idea of ropinirole. Only in hindsight can Drs. Cannon and Long characterize ropinirole as obvious.

**2. Secondary Considerations Confirm That The '808 Patent Is Not Obvious**

The non-obviousness of ropinirole hydrochloride (REQUIP) is further confirmed because of its commercial success and its fulfillment of a long felt need for additional Parkinsons Disease treatments. REQUIP was first approved in the United States on September 19, 1997, for the treatment of Parkinsons Disease and is among the drugs recommended by the American Academy of Neurology to be used as an initial monotherapy or as an adjunctive therapy for the treatment of Parkinsons Disease. In addition, REQUIP received priority review from the FDA and was approved for the treatment of RLS in May 2005. It is the first and only drug approved for treatment of RLS. This approval is evidence of REQUIP's safety and efficacy.

The mainstay of treatment for Parkinsons Disease over the last 40 years has been a compound called levodopa or "L-Dopa." Levodopa is a dopamine precursor that is absorbed by the brain and then is actually metabolized into dopamine. In a large number of patients, long-term treatment with levodopa is associated with the development of motor complications, such as *dyskinesias* and motor fluctuations. Patients with longstanding Parkinsons Disease develop intermittency of response and "off" periods when medication effects decrease, sometimes unpredictably. Factors related to the development of motor complications in Parkinsons Disease include the dose and duration of levodopa treatment and the progression of the disease. Accordingly, one common treatment strategy is to minimize the cumulative levodopa dosage employed over the course of the disease, particularly early on.

REQUIP has a longer half-life and more specific mechanism of action, so it does not lead to early onset of motor fluctuations and dyskinesias. REQUIP can be used on its own to treat

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

Parkinsons Disease in its early stages, and it can be used in combination with levodopa at all stages of the disease. In certain instances, REQUIP offers advantages over pramipexole, another dopamine agonist currently on the market as Mirapex<sup>®</sup>. REQUIP is eliminated from the body by the liver, while pramipexole is eliminated by the kidney. Depending on a particular patient's medical problems, one or the other of these drugs may be more appropriate. For example, ropinirole can safely be given to renal failure patients without dosage adjustment because it will have less of an effect on the kidneys than pramipexole.

Another advantage of REQUIP is its broad *dynamic range* (the dose range across which the drug can be used). The dynamic range of REQUIP is larger than that of pramipexole. Because REQUIP's dosage can often be increased with incremental benefit and in high dose ranges, ropinirole is more effective and better tolerated than pramipexole. As a result of these unique attributes, REQUIP fulfilled a long felt need for additional therapies for the treatment of Parkinsons Disease.

REQUIP has generated substantial revenues and profits for GSK and has been commercially successful.

**REDACTED**

The commercial success of REQUIP is due, in significant part, to use of the inventions claimed in the '808 patent in the production and sale of REQUIP. The '808 patent covers the active compound that delivers to a patient the benefits afforded by REQUIP. Absent use of the inventions claimed in the '808 patent, its sales would not have been possible. While other dopamine agonists are on the market, a substantial set of physicians and patients have concluded

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

that REQUIP offers the preferred treatment option available. Many of them choose to initially prescribe and purchase REQUIP, and then continue to do so.

**B. The '808 Patent Is Enforceable**

In prosecuting the '808 patent before the United States Patent & Trademark Office ("PTO"), the GSK patent department was consistent with its obligation to candidly disclose the information material to the claimed invention while obtaining the broadest claims possible under Title 35.

The broad generic claims asserted in the '808 patent by GSK are consistent with standard patent drafting custom and practice. Patent prosecuting attorneys are trained to draft and seek to obtain, broad *generic claims* which fairly reflect the contribution of the inventor to the art. In doing so, they routinely seek and are granted protection beyond the specific embodiment(s) discovered or developed by the inventor. With respect to chemical patents in particular, a patent limited to the precise compounds reduced to practice by an inventor would frequently be of little or no value because of the ability to obtain the same functionality of the compound by making minor changes to the molecule. Thus, it is normal and customary practice for a patent attorney to draft a patent application to include generic formulas that would encompass any related substituents that could reasonably be expected to exhibit similar activity, and to seek claims to such generic formulas.

**REDACTED**

No objection was made by the examiner to any *species* within the *genus* claim of the '808 patent on the basis that it did not have

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

utility. The patent examiner who examined the '808 patent had before him the genus disclosed in the '944 patent, which had been cited to the PTO by the applicant and which was the closest prior art. Given this disclosure, it would have been reasonable to conclude that the claimed genus of the '808 patent would possess the asserted utility.

The '808 patent's statement that cardiovascular effects of ropinirole were not subject to *tachyphylaxis* (tolerance over time) reflected GSK's knowledge at the time and was therefore truthful.

**REDACTED**

Moreover, the statement in the patent concerning tachyphylaxis is immaterial. Patentability of the compounds claimed in the '808 patent rested on their unexpected cardiovascular activity. See, e.g., '808 Patent, col. 1, lines 40-43. Whether that activity would be met with tolerance in animals or humans over time was not a basis of patentability in the specification.

As is typical in pharmaceutical patents, the '808 patent includes information concerning possible doses at col. 5, line 59 to col. 6, line 5. This passage does not falsely "suggest" that human testing was actually performed to determine the disclosed range of doses. Moreover, a mere "suggestion" cannot give rise to an inequitable conduct claim. First, it is clear that this passage in the '808 patent is a prophetic example because it is drafted in a properly used mix of present, future, and subjunctive tenses. Working examples describe experiments that have already been performed, while prophetic examples describe hypothetical experiments that could be performed in the future. Both are customary in the practice of drafting patents and the use of a past or present tense is sufficient to signal whether an example is of a working or prophetic nature. Further, because ropinirole was a new pharmaceutical compound at the time, the patent

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

examiner would have understood that the actual results of human testing would not have yet occurred because of the regulatory regime governing human clinical trials.

Finally, Dr. Paul Hieble, a pharmacologist employed at GSK at the time ropinirole was invented, was not named as an inventor because there was no basis for including him as such. He was not responsible for conceiving ropinirole, nor was he involved in its synthesis or the initial decision to test it for biological activity.

**C. The '860 Patent Is Not Obvious**

In 1987, a person of ordinary skill in the art at the time of the invention of the '860 patent would have been an individual with an advanced degree (M.S. or Ph.D.) in organic chemistry or pharmacology and having two or three years of laboratory experience in pharmacology in an academic or industry setting. A person without a graduate degree, but having more laboratory experience in this field, could also be considered a person of ordinary skill at the time of the invention. At the time of the invention, Dr. Owen had not specialized in dopaminergic compounds.

The idea that ropinirole could be a useful Parkinsons Disease treatment was not obvious at the time of Dr. Owen's discovery in light of the prior art. After it was determined that dopamine deficiency in the striatum was responsible for Parkinson's Disease, an era of discovery ensued in which drugs of many different chemical structures were synthesized in the hope that they would be effective in reversing the motor symptoms of Parkinson's Disease. One obstacle facing the development of dopamine agonists for the treatment of Parkinson's Disease or for other applications such as use in cardiovascular disease, was that the nature of the drug target, namely the dopamine receptor, was not well understood. For example, prior to 1979, only one dopamine receptor was generally believed to exist. At the same time, there was doubt over

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

whether a single dopamine receptor could explain all the behavioral, pharmacological and biochemical observations associated with dopamine receptors. In 1979, D-1 and D-2 receptors were identified, and in the years that followed, definitions and classifications of the types of dopamine receptor types changed repeatedly as scientists attempted to understand their nature and function. During the time period encompassing both patents, central dopamine receptors typically were referred to as D-1 and D-2 receptors, while peripheral receptors were termed DA-1 and DA-2 and it was widely believed that the brain and peripheral nervous systems contained different dopamine receptors. Accordingly, information derived from the study of peripheral dopamine receptors would not have been considered by the person of ordinary skill at the time to necessarily apply also to those receptors in the brain. It was known that some compounds had been shown to have effects on dopamine receptors in either peripheral tissues or in the brain, but not on both.

Another difficulty in designing drugs intended to act on the central nervous system is the need for the drug to cross "the *blood-brain barrier*." The blood-brain barrier is a membrane that controls the passage of substances from the blood into the central nervous system. At the time of the '860 patent, a person of ordinary skill would have known that alterations in molecules acting on dopamine receptors to increase the attraction of a compound to certain organic compounds such as fats (*lipophilicity*) would not necessarily result in activity in the brain. Ropinirole was known as a peripheral dopamine agonist with cardiovascular effects and the report of initial tests carried out on the compound suggested that it did not have central behavioral effects. Accordingly, a person of ordinary skill in the art would not have had a reasonable expectation that ropinirole would have a central nervous system effect and would be effective as a Parkinson's drug.

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

The results of GSK's behavioral testing of ropinirole also would not have caused an ordinary individual skilled in the art to conclude that the compound could have anti-Parkinson potential. Many experiments designed to measure the effects of dopaminergic drugs on the cardiovascular system are performed in organs that have been removed from animals or humans, and anaesthetized animals who are unconscious. This fact makes it impossible to detect motor changes relevant to an action on the brain or to Parkinsons Disease. When ropinirole was subjected to such tests, it was known to have a weaker interaction with the D-2 dopamine receptor than other dopamine agonists that had shown activity in Parkinson's Disease. This fact would have not made it an obvious candidate to be advanced through the drug discovery process. In light of this data, it would not have been expected that ropinirole would be developed for use as a drug for treating Parkinsons Disease.

To the extent that any alterations in animal behavior were able to be observed, these changes could have been attributed to many causes and were not considered to be necessarily reflective of either activity in the brain or the involvement of brain dopaminergic systems. One of ordinary skill in the art during this time period would have recognized that inhibition of locomotor activity in an animal behavioral test could be caused by *peripheral* actions unrelated to the dopaminergic system such as cardiovascular changes, muscle relaxant activity, or the induction of pain. In other words, an animal's movement could slow down simply because it is feeling poorly as a result of the chemicals that have been administered, not necessarily because a compound has crossed the blood-brain barrier. One of ordinary skill in the art would not have interpreted an inhibition of motor behavior as indicative of a central dopaminergic action relevant to Parkinson's Disease.

EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

**D. Secondary Considerations Confirm That the '860 Patent Is Not Obvious**

Claim 3 of the '860 patent encompasses the use of ropinirole for the treatment of Parkinsons. Ropinirole cannot be used for the treatment of Parkinsons without practicing the inventions claimed in the '860 patent asserted by GSK. For the majority of the period during which REQUIP has been available, the treatment of Parkinsons has been its central source of prescription volume. The commercial success of REQUIP discussed on pages 16-17 of this statement of intended proof is due in significant part to the inventions claimed in the '860 patent. REQUIP's commercial success as a treatment for Parkinsons Disease confirms that the '860 patent is not obvious.

**E. The '860 Patent Is Enforceable**

Dr. Owen is properly named as the sole inventor of the '860 patent because he was the first individual to have a firm and definite idea in his mind that ropinirole could be used as a treatment for Parkinsons Disease. :

**REDACTED**

The '860 patent does not suggest that any compound other than ropinirole had been actually tested for its anti-Parkinsons Disease effect. As with the '808 patent, GSK was nonetheless entitled to a genus claim of appropriate scope. The generic claim of the '860 patent that was sought and obtained by GSK is reasonable in light of the disclosure of the '860 patent and the prior art. Given the teaching of the '944 and '808 patents, it would have been reasonable, in light of patent prosecution custom and practice, to seek a genus claim in the '860

## EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

patent of substantially the same scope as the '808 patent and the '944 patent. However, the genus in claim 1 of the '860 patent is narrower at the 4-position than the genus claimed in the '944 or '808 patents. The fact that GSK drafted narrow genus claims appropriate for each patent reflects a careful and considered approach to prosecuting this family of patents.

The patent examiner who examined the '860 patent had before him the genus disclosed in the '944 patent and the '808 patent. Given the disclosure, it would have been reasonable to conclude that the claimed genus of the '860 patent would possess the asserted utility. Dr. Owen did not fail to disclose any material information with respect to the invention of the genus claims of the '860 patent and there is no evidence of an intent to deceive the Patent Office concerning inventorship of the generic claims of the '860 patent.

In the background section of the '860 patent, prior art *ergot alkaloids* compounds to treat Parkinsons Disease are described and criticized for their side effects. One of these compounds is bromocriptine, which is described as a "post-synaptic" dopamine agonist. The description of bromocriptine as "post-synaptic" is correct. The compounds of the '860 patent are indolones having a fundamentally different structure than ergot alkaloids. The basis of patentability was that these indolones had a central nervous system effect contrary to what was previously thought. The description of the ergot alkaloids and their side effects in the patent is solely as a predicate for the conclusion that there was a continuing need for effective treatments of Parkinson's Disease. Therefore, the statement regarding bromocriptine was not material and Dr. Owen did not make any false statements with respect to bromocriptine.

#### V. Conclusion

The '808 and '860 patents are valid and enforceable and Teva's actions constitute infringement of the '808 and '860 patents. Therefore, GSK is entitled to the following relief: (a)

EXHIBIT 25 TO PROPOSED PRETRIAL ORDER

a declaration that the '808 and '860 patents are valid and enforceable; (b) a declaration that a claim or claims of the '808 and '860 patents are infringed by the manufacture, use, sale, offer for sale or importation of ropinirole hydrochloride tablets by Teva and that Teva's submission of an ANDA is an act of infringement of the '808 and '860 patents; (c) an order providing the effective date of any approval of the Teva ANDA shall be a date which is not earlier than the expiration of both the '808 and '860 patents; (d) damages or other monetary relief to GSK if Teva engages in the manufacture, use, sale, offer for sale or importation of ropinirole hydrochloride tablets; (e) reasonable attorneys fees, filing fees, and reasonable costs of suit incurred by GSK in this action; and (f) such further and other relief this Court deems proper and just.